COMPARISON OF INTRAVENOUS RANITIDINE AND METOCLOPRAMIDE VERSUS INTRAVENOUS ONDANSETRON IN PREVENTING POSTOPERATIVE NAUSEA AND VOMITING POST GENERAL ANAESTHESIA

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CERTIFICATE

This is to certify that the dissertation entitled "*Comparison of Intravenous Ranitidine and Metoclopramide versus Intravenous Ondansetron in Preventing Postoperative Nausea and Vomiting Post General Anaesthesia*" is a bonafide research work done by *Dr. Mohsina Basheer* under my guidance and supervision in the Department of Anaesthesiology during the period of her postgraduate study for **M.D Anaesthesiology [Branch-X]** from 2012-2015.

Dr. G. Parvathy, DNB, DA,

[Guide]

Professor,
Department of Anaesthesiology,
Sree Mookambika Institute of
Medical Sciences [SMIMS],
Kulasekharam [K.K District],
Tamil Nadu -629161.

Dr. V.G. Jayaprakash, M.D,

[Co-Guide]

Professor,
Department of Anaesthesiology,
Sree Mookambika Institute of
Medical Sciences [SMIMS],
Kulasekharam [K.K District],
Tamil Nadu -629161.

Dr. G.Parvathy , DNB, DA

Professor and Head
Department of Anaesthesiology
Sree Mookambika Institute of
Medical Sciences
Kulasekharam
Kanyakumari (Dist) – 629161

Dr. Rema. V. Nair, M.D., D.G.O.,

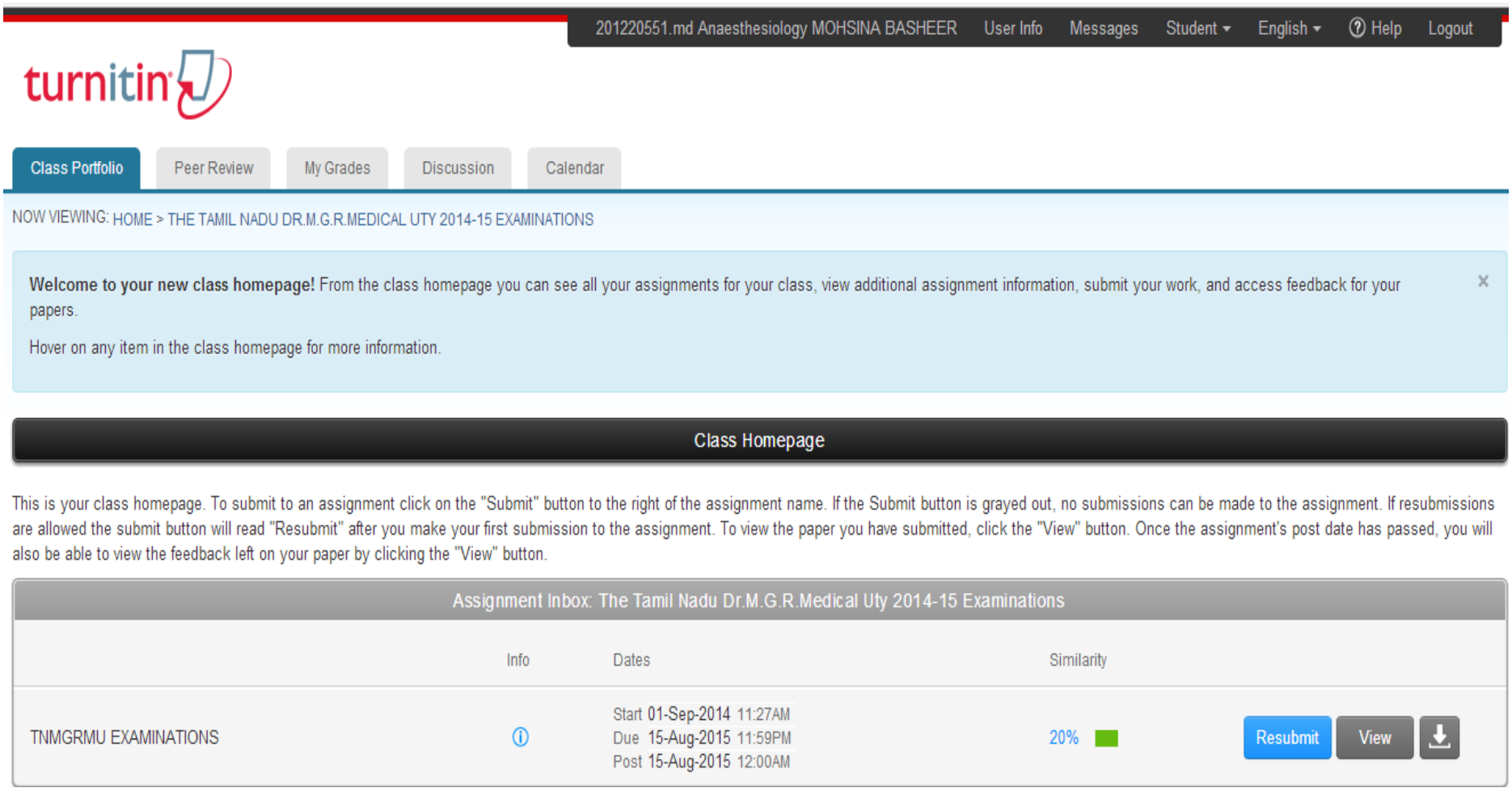
Director
Sree Mookambika Institute of
Medical Sciences [SMIMS]
Kulasekharam [K.K District]
Tamil Nadu -629161

DECLARATION

In the following pages is presented a consolidated report of the study "*Comparison of Intravenous Ranitidine and Metoclopramide versus Intravenous Ondansetron in Preventing Postoperative Nausea and Vomiting Post General Anaesthesia*" a randomized clinical trial, on cases studied and followed up by me at Sree Mookambika Institute of Medical Sciences, Kulasekharam from 2013-2014. This thesis is submitted to the Dr.M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of MD Degree examination in Anaesthesiology.

Dr.Mohsina Basheer,
Junior Resident in Anaesthesiology,
Department of Anaesthesiology,
Sree Mookambika Institute of Medical Sciences,
Kulasekharam, Kanyakumari District.

PLAGIARISM SCREENING REPORT



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Dr. Mohsina Basheer.

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LIST OF ABBREVIATIONS

IM	:	Intramuscular
IV	:	Intravenous
RCT	:	Randomized control study
POV	:	Postoperative vomiting
PONV	:	Postoperative nausea and vomiting
CTZ	:	Chemoreceptor trigger zone
CNS	:	Central nervous system
EPS	:	Extrapyramidal syndrome
ASA	:	American Society of Anaesthesiologists
NIBP	:	Non-invasive blood pressure
$ETCO_2$	:	End tidal carbon dioxide
ECG	:	Electrocardiogram
GABA	:	Gamma amino butyric acid
NSAID	:	Non-steroidal anti-inflammatory drug
TDS	:	Ter Die Sumendum
D	:	Dopaminergic
M	:	Muscarinic
H	:	Histaminergic
HT	:	Hydroxytryptamine
OR	:	Odds ratio
N_2O	:	Nitrous oxide

ABSTRACT

Background and Objectives:

Postoperative nausea and vomiting (PONV) have forever been a complication of anaesthesia. Lack of efficient prophylactic antiemetic therapy may prove detrimental to a successful surgery and timely discharge. There are a wide range of drugs for preventing PONV. This study was designed to compare the efficacy of intravenous ranitidine plus metoclopramide to that of intravenous ondansetron in preventing post-operative nausea and vomiting in patients undergoing general anaesthesia.

Methods:

84 patients undergoing elective surgery under general anaesthesia were randomized into two equal groups to receive either a combination of 50 mg ranitidine plus 10 mg of metoclopramide or 4mg of ondansetron. Both groups of drugs were given intravenously half an hour prior to induction. All patients underwent standardized general anaesthesia with controlled ventilation. They were monitored at the initial first hour and for 24 hours post operatively for episodes of nausea, retching and vomiting which were tabulated under a scoring system.

Results:

When considering ranitidine and metoclopramide group: nausea was absent in 71.43% of patients in the initial hour and 90.48% of patients in the 24 hours post operatively. Retching was absent in 90.48% of patients in the initial hour and in 95.24% of patients in 24 hours post operatively. Absence of vomiting was seen in 76.19 % of patients in the initial hour and in 95.24 % of patients in the 24 hours of postoperative period.

In the ondansetron group nausea was absent in 71.43 % of patients in the initial hour and in 88.09 % of patients in 24 hours of postoperative period. Absence of retching was seen in 83.33% of patients in the initial hour and in 97.61% of patients in 24 hours of postoperative period. Absence of vomiting was seen in 85.71% of patients in the initial hour and in 92.85% of patients during 24 hours of postoperative period.

Conclusion:

It was concluded from this study that the combination of ranitidine 50 mg, metoclopramide 10 mg was as efficient as ondansetron 4mg when given intravenously prior to general anaesthesia in preventing PONV.

Key words:

PONV; general anaesthesia; ranitidine; metoclopramide; ondansetron.

INTRODUCTION

Anaesthesia and surgical procedures are associated with a number of post-operative symptoms which leads to patient dissatisfaction with anaesthesia[1].The most common of these symptoms include: pain, dizziness, drowsiness, headache, nausea and vomiting. However the most common and distressing of the symptoms is pain and emesis. While it is true that lot of attention has been paid towards relief of pain, not much attention has been paid to the problem of postoperative nausea and vomiting[4]. But postoperative nausea and vomiting is estimated to be a more critical and distressing symptom to the patient. Sometimes nausea and vomiting may exist even after minor and ambulatory surgery which would eventually delay the hospital discharge and leave a dreadful experience of surgery and anaesthesia with the patient. The situation can be so grave that it is estimated that most patients are willing to pay up to $100 for an effective treatment[1].

Nausea and vomiting have always prevailed with anaesthesia and one of its first extensive descriptions was given by Sir John Snow in 1848 itself. In Ether era, the incidence of PONV had been around 75-80%[2]. In recent large studies the incidence is stated to be around 25-30 %[2, 3]. In Laparoscopic procedures the incidence may range up to 53-72 %[2, 3].

The occurrence of PONV poses a challenge for surgeons and anaesthetists alike and hence it is very rightly termed as “BIG LITTLE

PROBLEM" [5]. The problem is further aggravated by the fact that there is no "magic bullet" that will prevent or control PONV in all aspects and in all patients.

The consequences of post-operative nausea and vomiting may be mild, moderate or severe. While mild and moderate forms may just increase patient dissatisfaction, the more severe forms of nausea and vomiting not just increases the patient dissatisfaction, but causes also dehydration, electrolyte imbalance, dehiscence of wound, prolonged bleeding from surgical site, esophageal rupture and blindness. In the post-operative period the major danger possessed by PONV is aspiration of vomitus leading to respiratory obstruction and aspiration pneumonia. All these not only lead to an increased use of medical resources but also consequent delay in discharge from hospital [4].

With the change in trend from an inpatient to outpatient care and with the trend towards hospital and office based medical and surgical enhancement, the attention towards treatment of PONV has been on the increase[5].

PONV being multifactorial has been extensively studied and it is shown to have a decreased incidence in the recent times because of the refinement in surgical procedures, identification of the high risk patients, use of improved pre and post anaesthetic agents and by using less emetic agents. Even after all these precautions PONV still continues to be one of the greatest nuisance of post anaesthesia, with the only rescue being pharmacological management.

There are a wide range of antiemetics available to date which have evolved over the eras. These include dopamine [D_2] receptor antagonists, Histamine [H_1] receptor antagonists, Muscarinic antagonists, Cholinergic receptor antagonists, $5HT_3$ receptor antagonists, alpha adrenergic agonist, corticosteroids, benzodiazepines, benzamides, propofol and butyrophenones[2].

Ondansetron is a $5HT_3$ receptor antagonist which is being used widely for the management of PONV and belongs to the newer era of drugs for PONV treatment. But for many years anaesthetists have placed their trust on the combination of ranitidine/metoclopramide as a preventive therapy for PONV.

This study was carried out for comparing the effectiveness of these 2 groups of drugs in reducing and preventing the incidence of PONV in patients undergoing General anaesthesia.

AIMS AND OBJECTIVES

To compare the efficacy of ranitidine plus metoclopramide to that of ondansetron in controlling postoperative nausea and vomiting in patients undergoing general anaesthesia.

REVIEW OF LITERATURE

One of the earliest and extensive reports on the phenomenon of post-operative nausea and vomiting had been given by John Snow as early as 1848, just about 18 months after the introduction of chloroform into anaesthesia. Historically important modes of treatment included agents like wine also which was a preferred agent by the patients. The Battleys solution of opium has also got historical importance[4].

The ether era had the highest incidence of PONV, where its incidence ranged as high as 75-80%[2,3]. During this era they employed a number of techniques to prevent PONV. These included olive oil and insulin-glucose infusions. Robert Ferguson was the first to use olive oil in 1912, which he administered by mouth after the patient had gained partial consciousness. The idea behind this was that oil would absorb any residual ether that might be there. Brown Sequard in as early as 1883 had established the benefit of atropine in controlling postoperative nausea and vomiting when morphine was used[4].

The change in anaesthesia techniques and the switch over from opioids (and deep ether anaesthesia) to a non-opioid (or supplemented opioid premedication) and the usage of lighter (non-ether) anaesthesia had eventually led to a decrease of PONV up to 50%[4]. The refinement in the surgical techniques and the better identification of the at risk patients of PONV have also led to a decrease of PONV[4]. And now the incidence is at 25-30% [2,3].

About seventy five years ago Flagg had suggested that PONV may result from causes which were not entirely anaesthesia related and he also suggested that there are at least three different kinds of vomiting. The first of these may be attributed to the anaesthetics such as ether, the second may be due to reflex responses and the last may be due to opioids. Subsequent studies over a period of time have established a large number of non anaesthetic factors behind the pathogenesis of postoperative nausea and vomiting[4].

Over the years a number of drugs have been developed to treat postoperative nausea and vomiting. One of the earlier drugs to be produced for the treatment of PONV was the Phenothiazines. Phenothiazines were synthesized originally in 15th century by the dye industry chemists. Promethazines were synthesized in 1930 and was found to be beneficial in controlling emesis [4]. Chlorpromazine was synthesized by Charpentier in 1949, though it had anti-emetic property, its use was limited due to its side effects of sedation and hypotension. Perphenazine and Prochlorperazine are other drugs extensively used in the management of PONV[4].

There has been a volley of systemic reviews in the world literature which dealt with PONV. However still to this date there is no specific management for PONV which would be ideal to all patients. Ever since the Halothane times, in 1956 there has been a little change in the PONV[4].

So now the question is why the absolute mechanism or the absolute remedy to this wide spread and big little problem is not known? There are four factors to explain this[4]:

1. **Complexity of the problem**:

The variables and factors associated with PONV are so many, such that to study them independently and to assess the effects of an intervention would require a large number of patients and a large number of well controlled trials.

2. Inadequate quantification of the problem:

Though there have been a large number of clinical trials, none of them have accurately quantified the problem in terms of nausea, vomiting or retching.

3. Inadequate antiemetic regimen:

Emesis occurs as a common symptom in disease or as a side effect of therapies e.g. cytotoxic chemotherapy, radiotherapy. It can also be a naturally occurring phenomenon in motion sickness and pregnancy. The physiology of the emetic mechanism is not well researched. The predominant mechanism of each type of nausea and vomiting should be identified for its effective antiemetic treatment.

4. **Animal Model :**

The lack of adequate animal study model, limits the study of physiology and pharmacology of the mechanism of PONV. Many species of experimental animals such as rats and rabbits do not vomit upon stimulation. However monkeys and dogs do react to the same range of

emetic stimuli as men especially with cytotoxic drugs and radiation. However they cannot be stimulated to suffer from pregnancy, motion sickness and post-operative and post-anaesthetic emesis. So now the question arises why this much importance is given to this little problem. This is because of the consequences that are produced by PONV which may be classified into physical, metabolic and psychological[9].

Physical

Retching and vomiting are fairly violent activities which may cause stress and strain on certain structures if they are present for a prolonged amount of time. Results of such stress can lead to oesophageal tears leading to mediastinitis and may also lead to Boerhaave Syndrome and Mallory Weiss Syndrome (that is the rupture and hemorrhage of the oesophagus respectively), rib fractures can also occur, rupture of the cutaneous vessels in the upper body, fatigue and strain of muscles can occur and gastric herniation can also occur. There may also be wound dehiscence and bleeding at the operative site which may lead to hematoma formation. There may also be undue increase in the intracranial pressure and intraocular pressure. In case of plastic surgeries there may be bleeding from skin flaps. The strain and stress on wound may eventually lead to an increase in the postoperative pain. Another fatal complication of PONV is aspiration of vomitus which may lead to aspiration pneumonia and may also trigger the cardiorespiratory reflexes and thereby increase the chance of morbidity and mortality[9].

Metabolic

With persistent vomiting, dehydration, fluid and electrolyte imbalance may occur especially when considering the pediatric age group[9].

Psychological

Patients may be so distressed by the presence of PONV that it may produce a general aversion to surgery and anaesthesia. The patient may expect the same complication to occur with subsequent surgery. The eventual consequence of PONV is delayed hospital discharge and this will consequently increase the financial burden because the patient will require more time in the recovery room and need more care from the medical faculty. This will eventually put a burden on the patient as well as the health system as a whole[9].

Postoperative nausea and vomiting (PONV) became a commonly known and studied phenomenon after the landmark review by Watcha and White [2] in which they explained its etiology, treatment and prevention.

PHYSIOLOGY OF NAUSEA AND VOMITING

Following are the definitions of each associated term:

1. Nausea:

Nausea is a subjective, unpleasant sensation of a need to vomit and the feeling that vomiting is imminent. It occurs in waves either preceding vomiting or in isolation.

2. Retching:

This is an expulsive muscular effort with spasmodic rhythmic contraction of diaphragm, chest wall and abdominal wall muscles but without the actual act of expulsion of stomach contents [2,3]. These are also called as 'dry heaves'.

3. Vomiting:

This is the forceful expulsion of upper gastro intestinal contents through mouth which is brought about by the powerful and sustained contraction of abdominal muscles, descent of the diaphragm and the subsequent opening of the upper esophageal sphincter. Vomiting is different from gastroeosophageal reflux or regurgitation. Gastroeosophageal reflux or regurgitation are neither forceful nor do they involve the muscular activity as in retching or vomiting.

Vomiting is actually a naturally occurring defense mechanism of the gastrointestinal system which is brought in action on ingestion of toxins and irritants .It aims to reduce the further intake of the toxins. But clinically vomiting (especially the postoperative nausea and vomiting) is considered as undesirable mainly because of the consequence they produce.

Why should anaesthesia and surgery induce nausea and vomiting? The reason for this is just like in many other clinical situations where nausea and vomiting can occur, some aspects of surgery and anaesthesia can also trigger the emetic detectors.

MECHANISM OF NAUSEA AND VOMITING:

The mechanism of vomiting has 3 major components[4] :

I. Emetic detectors

II. Integrative mechanism

III. Motor outputs

I. **Emetic Detectors**[4]:

These are detectors located in gut, chemoreceptor trigger zone and elsewhere which upon stimulation sends activated impulses leading to emesis within 20 seconds. The detectors are the following:

Abdominal Visceral Afferents:

These are the detectors present in the gut. They are vagal afferents and are of two types:

a. ***Mechano receptors***:

They are located in the gut muscular wall. These get activated when there is contraction and distention of the gut as in times of overeating, surgical manipulation and physical damage.

b. ***Chemoreceptors:***

These are located in the mucosa of upper gut and are very sensitive to the chemical stimuli of the intraluminal environment. They respond to stimuli such as mucosal stroking, acid, alkali, temperature, toxins (e.g. staphylococcal entero toxin) and other noxious chemical stimuli. The substrate for the polymodal mucosal receptors is not well known but it is postulated that an arrangement like that of the taste buds or the carotid body, (having detector cells) is present which responds to a range of

stimuli by releasing the neurotransmitter. In the intestine enterochromaffin cells acts as detector cells[4].

Area postrema receptors:

Another detector which is one of the most important anaesthesia associated detector lies in the area postrema. The area postrema is a U shaped circumventricular organ of the brain which is a highly vascular area. It lies at the caudal part of fourth ventricle and contains the specialized cells termed as chemoreceptor trigger zone (CTZ). Wang and Borison were the first to demonstrate the chemoreceptor trigger zone. CTZ is deficient in blood brain barrier which makes it ideal for detecting the blood borne toxins / drugs or the circulating toxins in the CSF. It then activates the vomiting centre in the medulla. The area postrema is rich in dopamine opioid and serotonin receptor ($5HT_3$). The CTZ contains abundant opiate receptors, enkephalins, $5HT_3$ receptors and also dopamine receptors. This zone is said to be responsible for the vomiting stimuli associated with opiates, cardiac glycosides and motion sickness. They receive afferent inputs from vagal and glossopharyngeal nerve which provides the information on lung volume, gut content and blood pressure[4].

Nucleus solitarius is another detector lying close to vomiting centre which is rich in encephalin, muscarinic, cholinergic, histamine receptors. All these receptors can transmit impulses into the emetic centre. Hence the blockade of all these receptors is the most important mechanism used in the current antiemetic drugs

Vestibular system:

Vestibular labyrinthine is involved in the nausea and vomiting occurring during motion sickness. They induce vomiting by motion stimuli which is conducted by the eight cranial nerves. The possibility of labyrinthine stimulation should be borne in mind while the patients are shifted onto the trolleys for transportation after surgery because this may act as additional input to induce emesis.

There is only patchy evidence if labyrinthine system has any association with drug induced nausea and vomiting

Higher influences:

The exact mechanism of the influence of the higher centres in nausea and vomiting is unclear but there is little doubt that these centres (e.g. Limbic system) do have a role in inducing nausea and vomiting. Impulses from higher centre (e.g.: limbic system) and visual cortex can cause vomiting by having a more of facilitatory role in stimulating the brain stem emetic centre and seems to have little role as the primary detectors of the emetic stimuli.

Miscellaneous inputs[(4)]:

Nausea and vomiting maybe easily brought about by activation of many other parts of the body:

1. Unpleasant tastes can induce both nausea and retching. However it is not clear if this is due to a primary response or is a secondary response in association with previous illness and thereby a result of prior experience (learned aversion).

2. Nausea and gagging can also be brought about by the mechanical stimulation of the pharyngeal afferents brought to the brain stem by the glossopharyngeal nerve.
3. Ventricular cardiac afferents may also induce nausea and vomiting and this may be the underlying reason for nausea and vomiting found before or during myocardial infarction.
4. Tympanum can be stimulated which in turn activates auricular branch of vagus called as the Arnold's nerve or the Alderman's nerve, which induces nausea and vomiting

The inputs from all these centres are brought to the vomiting centre where they undergo integrative mechanism. Before moving onto the integrative mechanism the vomiting centre is considered briefly:

It is generally accepted that a discrete area located at the reticular formation of the medulla acts as the vomiting centre and is responsible for controlling and coordinating nausea and vomiting. A complex range of interactions occur here which eventually results in vomiting which is a complex reflex. The interactions occurring here involves the reticular formation along with other areas like the nucleus tractus solitarius and the autonomic nuclei especially the vagus nerve. Along with this the vomiting centre also receives the afferent inputs from the receptors in the gastrointestinal tract, peripheral pain receptors (which are activated during trauma), the pharynx during the gag reflex, vestibular system (which are stimulated during motion sickness), the chemoreceptor trigger zone (which is activated by drugs/toxins) and finally the cerebral cortex.

Some 40 neurotransmitters are involved in the neurochemistry of the vomiting centre, which makes the process of controlling nausea and vomiting even more difficult.

II INTEGRATIVE MECHANISM[4]:

Vomiting is a motor programme which requires an integrative mechanism involving coordination between many physiological, autonomic and somatic components. The coordination of motor components occurs in the brain stem. This seats the vomiting centre in the medulla oblongata. The vagal motor neuron supplying the gut and heart originate in the brain stem at the dorsal motor vagal nucleus and nucleus ambigus. Also the dorsal and ventral respiratory groups regulating the phrenic nerve output from the cervical spinal cord are located here and so are the presympathetic neurons which regulates the sympathetic tone in the blood vessels and heart .The coordinated output of these nuclei produces the characteristic vomiting pattern[4].

III MOTOR OUTPUT[4]:

Vomiting is a motor event involving both the autonomic and somatic division. Though ejection of upper GI contents is the most obvious component of vomiting, it actually occurs after going through a series of motor events. It consists of three phases:

Preejection phase[4]:

This is associated with a sense of nausea with several visible signs such as cold, sweating, pupillary dilation, cutaneous vasoconstriction, tachycardia and decreased gastric secretion. These are all mediated by

sympathetic nerves. There is also salivation which is due to parasympathetic stimulation.

Just before the ejection phase there is relaxation of the proximal stomach. This is brought about by the action of vagal efferent nerves which stimulates the post ganglionic neuron in the stomach wall to release neurotransmitters like vasoactive intestinal polypeptide (VIP) or nitric oxide. The next event is retrograde giant contractions which propels contents from the mid small intestine towards the stomach. This is also under the vagal control and is mediated by the neurotransmitter acetylcholine. The gastric relaxation confines the gastric contents to the stomach while the retrograde giant contractions helps load all the contaminated gastric contents in the stomach ready for ejection. The pre-ejection phase may or may not be followed by the ejection phase[(4)].

Ejection phase[(4)]:

This phase consists of retching and vomiting, with the expulsion of gastric contents occurring only during vomiting.

The phenomenon of retching can be explained as rhythmic and synchronous contraction of diaphragm and abdomen. As the antral portion of the stomach contracts, the proximal portion relaxes leading to oscillation of contents between the stomach and oesophagus. The hiatal portion of diaphragm does not relax during retching. There is increase only in the intra-abdominal pressure with a decrease of intra thoracic pressure during retching.

During vomiting however, hiatal portion of diaphragm relaxes and also abdominal muscles contract forcefully. Thus the actual gastric contents expulsion occurs by compression of stomach between the descending diaphragm and the contracting abdominal muscles and along with this the lower esophageal sphincter relaxes .There is increase of both intrathoracic and intragastric pressure along with reverse peristalsis which leads to expulsion of gastric contents through the open mouth .

Post ejection phase:

This involves autonomic and visceral responses that returns the body back to quiescent phase with or without nausea[4].

FACTORS RESPONSIBLE FOR PONV

Factors responsible for postoperative nausea and vomiting may be broadly divided as two:

I)Non anaesthetic factors

This again consists of A) patient factors and B) procedure factors

II). Anaesthetic factors:

This again consists of A) the experience of the anaesthetist B) preanaesthesia period C) gastric suction D) intubation E) anaesthetic technique F) post-operative period.

NONANAESTHETIC FACTORS

A. PATIENT FACTORS:

Susceptibility

Susceptibility or higher predisposition of some patients to vomiting even with slightest stimulation is an established factor for PONV. It was

observed by Purkis that the chances for PONV had been increased up to three folds in patients with previous history of PONV. This may be due to psychological factors in some while in others this may be due to a variation in the development of the vomiting reflex [2,3,6].

Sex

Emetic symptoms are about 2-4 times more common in females. This holds true even for postmenopausal women over 65 years. The symptoms may also be more severe in the female patients than in the male patients. This high incidence of PONV in women is probably due to female hormones. The variations in the plasma progesterone and serum gonadotropin may be responsible for this. The incidence is higher in the luteal phase and is maximal on the 4^{th} and 5^{th} day of the menstrual cycle. This gender difference does not hold much significance beyond the eight decade of life, again suggesting the role of gonadotropins in the greater incidence of PONV in women[2,3,6].

Age

PONV incidence changes with age. In infants the incidence may only be about 5%, it may increase to 20% in children below 5 years, while the incidence may increase up to 34-51% in the late childhood (6-16 years) thereafter it may remain constant or may decrease to 14 -40% during the adult hood[1,2,6]. In general children are twice as likely as adults to experience PONV.

Weight

There is a positive correlation between PONV incidence and body weight. Obese patients have higher incidence of PONV. This is because:

1) The adipose tissue acts as a reservoir that loads the inhalational anaesthetic agents, which is eventually released back into the blood stream even after stopping the supply.
2) Also obese patients have a larger residual gastric volume and an increased incidence of gastro esophageal reflux. They also have greater chance of gallbladder and other gastrointestinal diseases, all of which may predispose the obese patients to greater incidence of PONV.
3) Compared to the non-obese patients, obese patients are well documented to have difficult airways and hence they have greater chances of gastric inflation during attempted face mask ventilation to maintain saturation[2, 3, 7].

History of Motion Sickness and or Previous PONV

Patients with previous experience of PONV are three times more likely to experience PONV again. Patients susceptible to motion sickness are also prone to PONV[2].

Anxiety

Preoperative anxiety leads to increased incidence to PONV. The alpha adrenergic stimulation has been postulated as an explanation for this phenomenon. Anxious patients swallow excessive amounts of air

before surgery leading to an increased gastric volume which may predispose for post-operative emesis [2].

Gastroparesis

Delayed gastric emptying secondary to underlying disease may increase the risk of PONV. These conditions include gastrointestinal obstruction, pyloric stenosis, chronic cholecystitis, intrinsic neuropathies, neuromuscular disorders and myopathies. Gastric hypomotility complicates conditions like progressive muscular dystrophy, amyloidosis, scleroderma, anaemia, increased abdominal pressure, familial visceral myopathies and pregnancy. Along with gastroparesis patients with diabetic mellitus may also be associated with pylorospasm, isolated antral hypomotility and hence diabetic patients have an increased incidence of PONV. Premedication with opioids and barbiturates given for anxiolysis may lead to delay in gastric emptying thereby predisposing to post-operative emesis.

Smokers

Nonsmokers are at least two times more prone to postoperative nausea and vomiting when compared to smokers. This possibly reflects on the nicotine induced increases in the synaptic concentration of dopamine via GABA-ergic pathway inhibition[2,3].

Pregnancy

The entire gastrointestinal tract undergoes changes during pregnancy. There is gastric hypomotility, increased secretions, along with

a relaxed gastroesophageal junction during pregnancy all of which increases the incidence of regurgitation and PONV.[1,2,4,6]

B. SURGICAL/ PROCEDURE RELATED FACTORS:

General effects:

Gastrointestinal motility: The anesthetic agents used already reduce the gastrointestinal motility, the surgery also has a similar effect and it outlasts the duration of surgery. The end result of combined effect of anaesthesia and surgery is a twofold reduction in the gastric emptying. Due to surgery induced delayed gastric emptying there will be accumulation of secretions and this may induce reflux of bile into the stomach and there may also be gas accumulation which may be accounted to anaesthetic technique, air swallowed before surgery or may be endogenously produced. All these may eventually lead to the activation of gastrointestinal visceral afferents including nociceptors (in case of a strong stimulus). When the patient regains consciousness, the distensile stimuli will cause upper abdominal discomfort which may lead to nausea or vomiting. The effects of surgical trauma will persist beyond the surgery period and may extend into the postoperative period. Therefore though patient has recovered from anaesthesia, they may still have a reduced gut motility and therefore maybe unable to cope with a normal meal [2,3,6,10].

Endocrine effects:

Apart from adrenaline, another hormone released due to surgical stress response is vasopressin (AVP) which has a close association with nausea rather than vomiting[10].

Site of Surgery

The type of surgical procedure influences the incidence of PONV irrespective of the anaesthetic technique used. Considering the adult population the highest incidence of PONV was reported in women undergoing laparoscopic ovum retrieval procedures which are estimated to be about 54%. This is followed by laparoscopy having an incidence of 34%, dental extractions having an incidence of 16%, dilation and curettage of uterus having an incidence of 12% and knee arthroscopies with an incidence of 22%. High incidence of PONV has also been observed after extracorporeal shock wave lithotripsy, stomach, duodenum and also gallbladder operations. Ear surgery, eye surgery (e.g. Strabismus surgery), plastic, oral and head and neck surgery also have higher chances for increased PONV [2, 3, 6].

Duration of Surgery:

Patients having a long duration of surgery, i.e., more than 3 hours have a greater incidence of post-operative emesis. This is because during a longer surgery, there is a simultaneous longer period of exposure of patients to lipid soluble, emesis producing inhalational agents and intravenous agents[2, 3, 6].

Reasons for Surgery:

In some patients nausea and vomiting are already a component of the disease for which they are being treated (e.g.. raised intracranial tension, G.I obstruction). In these patients the emetic centres will already be in a sensitized state [2, 3, 6]

II. ANAESTHESIA RELATED FACTORS

A. Experience of the anaesthetist:

Vigorous positive pressure ventilation during facemask ventilation causes increased gastric dilation and will predispose a patient to PONV. This commonly occurs in hands of an inexperienced anaesthetist and in obese patients in whom mask ventilation may prove difficult[2,4].

B. Preanaesthesia including preoperative fasting and premedication.

Preoperative Fasting:

A 6-8 hour fasting period is mandatory to reduce the risk of aspiration of gastric contents during induction because ingestion of solid food causes distention of the gut and increases the release of hormones sensitizing the vomiting reflex. Intake of food shortly before the induction of anaesthesia is a well-documented reason to cause emesis both intra-operatively and post-operatively. The volume and chemical composition of the meal taken influences the rate of gastric emptying, with fatty meals being emptied relatively slowly. Moreover, any associated trauma may further lower the gastric emptying due to sympathetic activation. Food activates the abdominal vagal afferents and

this effect which when combined with the effect of anaesthesia on the CNS may stimulate the emetic reflex[2, 3, 6,11].

Preanaesthetic Medication:

Premedication using opioids increase the incidence of PONV by stimulating opioid receptors regardless of the route of administration. Opioids can directly stimulate the area postrema to a great degree and increase the incidence of PONV. However with higher doses opioids can depress the CNS and the vomiting centre. Opioids can also decrease the gastrointestinal motility, prolonging the gastric emptying time and thereby increasing the chances of PONV. Opioids also enhance the release of serotonin from the small intestine and hence contribute to PONV. Opioids can also increase the release of vasopressin (ADH) from posterior pituitary, which is not only associated with nausea and vomiting, but also has an inhibitory effect on gut motility[3,6,10,11].

Opioids can sensitize the otic and vestibular areas and hence predispose to PONV. Stimulation of endolymph present in the inner ear due to patient movement postoperatively can increase the frequency of opioid induced emesis. Therefore during movement of patients from cart to chair, chair to standing, ambulation or during car ride back home can all increase chances of PONV in outpatients. These side effects may last up to 6 hours after opioid administration[3,6,10,11].

Scopolamine (hyoscine) or atropine given along with opioids as premedication reduces the incidence of PONV in comparison to opioids being used alone. Both atropine and scopolamine being tertiary amines

cross the blood brain barrier and can hence exert their antiemetic and antimotion sickness effects. Glycopyrrolate being a quaternary amine does not cross the blood brain barrier and hence does not have any antiemetic or antimotion sickness effects. Scopolamine rather than atropine is most routinely combined with morphine as premedication as it has greater sedative effects. [3, 6]

Benzodiazepines, e.g., midazolam are used as premedication for sedation because they decrease the release of catecholamine and hence decrease the incidence of PONV.

C. Gastric Distension and Suctioning:

Nasogastric suctioning is done to remove secretions, blood and air from stomach. Surgeries involving mouth, nose, oropharynx may lead to swallowing of the blood. Blood in stomach is a strong emetogenic stimulus and is difficult to be treated by just giving antiemetic medication alone. The removal of this blood by gastric suction or emesis helps in providing relief [2, 3].

Also in cases of gastric distension (i.e. in GI obstruction, ileus) gastric suction decreases PONV. PONV following GI surgery or air inflation into the stomach, as occurring during vigorous mask ventilation can be reduced by using gastric suctioning. Presence of oral airway, pharyngeal suctioning or a continuous presence of nasogastric tube in postoperative period stimulates the gag reflex and leads to increased gagging and retching due to stimulation of glossopharyngeal nerve and eventually increases the chance of PONV [2, 3, 8].

D. Intubation

During the insertion of the airway device through the oropharynx, the pharyngeal afferents (predominantly the glossopharyngeal nerve) may be stimulated. This stimulation can induce gagging reflex and can also cause retching and vomiting[11].

E) Anaesthetic Techniques:

1. **General Anaesthesia:**

a) IV Induction agents:

Different IV induction agents are associated with differing degrees of PONV. Agents producing smoother recovery (i.e., Thiopentone, Propofol) have a lower incidence of PONV when compared to rapid recovery producing agents (methohexital) and also from those producing higher incidence of excitatory effects during or after anaesthesia (e.g., etomidate, ketamine). Thiopentone when used with Nitrous Oxide in minor gynaecological surgery have an incidence of PONV of 12%. Etomidate used in the form of continuous infusion during balanced anaesthesia increases the incidence of PONV[2, 3].

Ketamine when used for induction and or maintenance of anaesthesia have higher chances for PONV than when thiopentone and nitrous oxide are used. This is due to release of endogenous catecholamine.

Propofol is frequently used for total intravenous anaesthetic technique and have proved to lower the incidence of PONV. Propofol is structurally unrelated to any of the other available intravenous agents.

Therefore propofol is very popular during outpatient procedures because of its smoother recovery characteristics including rapid emergence and a lower incidence of PONV[2, 3, 6]. The incidence of PONV is as low as 1-3% as compared to the 10-15% found with the other agents. However studies have shown when propofol is used in a Propofol-nitrous-oxide-inhalation agent combination, the incidence of PONV is relatively higher than when used alone [2, 3].

b. Inhalational anaesthetic agents:

Nitrous oxide

Nitrous oxide is associated with a high incidence of PONV ranging from 49% to 67% depending on the percentage of end tidal concentration. Nitrous oxide stimulates PONV by the following three mechanisms:

1. Direct stimulation of vomiting centre by interacting with opioid receptors and stimulation of the sympathetic nervous system by releasing catecholamine.
2. Middle ear pressures may be changed resulting in traction of the round membranous window leading to vestibular system stimulation.
3. Distension of air containing spaces like stomach, large and small intestines and gall bladder.

There is significant increase of PONV incidence in patients being anaesthetized with a balanced anaesthesia technique containing nitrous oxide/ opioid/ oxygen/ muscle relaxant than with those patients

anaesthetized with an inhalational technique. The incidence of PONV is still lower when total intravenous technique is used [2, 3].

Volatile anaesthetic agents:

Older anaesthetic agents like diethyl ether or cyclopropane have higher incidence of PONV ranging up to 75 – 85%. The newer inhalational agents like halothane / isoflurane/ enflurane/ desflurane and sevoflurane have a lower incidence of PONV. This is associated to the release of endogenous catecholamines [2].

c) Neuromuscular blocking agents:

Neuromuscular blocking agents do not have much effect on PONV but the reversal agents i.e. the anticholinesterase drug (e.g. neostigmine) and anticholinergic drugs like atropine and glycopyrrolate is associated with a higher incidence of post-operative emesis and nausea. When anticholinesterases are used alone, there is a further increase of PONV incidence because these agents will increase the gastric motility. The increased bowel activity is unchanged by the anticholinergic agent (be it atropine or glycopyrrolate) used in combination with the anticholinesterases [3]. However when the combination of anticholinesterases and anticholinergic drugs are used in the usual doses emesis usually does not occur[3].

Balanced anaesthesia:

Compared to the use of total intravenous or inhalational techniques, the use of nitrous oxide – opioid relaxant technique is found to have a greater incidence of PONV. This is greatly attributed to the administration

of opioid – nitrous oxide combination and a direct effect of these agents on CTZ. Morphine, in its analgesic doses does not cause much nausea in the recumbent position but however have an emetogenic effect upon the movement of patient due to a vestibular component to opioid induced emesis. This analgesic induced emesis may be decreased if an alternative drug such as Non-steroidal anti-inflammatory drugs can be used. Ketorolac (NSAID) can be effectively used in place of morphine or fentanyl especially in the outpatient setup[(2)].

2) Spinal / Epidural Anaesthesia (central neuraxial blockade)

Spinal anaesthesia is associated with a PONV incidence of 10 – 20%. The factors associated for higher incidence of PONV are:

Height of the blockade:

When the block extends to or above the T_4 dermatome, it is associated with a higher incidence (3.9 times greater) compared with a lower level block. This is related to a greater sympathetic blockade, which will lead to an unbalanced parasympathetic influence.

Pain :

Appreciation of pain during surgery increases the incidence of PONV.

Hypotension :

When the arterial blood pressure declines rapidly to less than 80 mmHg or decreases to more than 40 mmHg from baseline blood pressure occur, it is often associated with nausea. It is postulated that this is due to hypoxemia at the vomiting centre because this event could be

attenuated by administration of 100% oxygen. Also the use of IV atropine decreased the emesis associated with hypotension suggesting that vagal stimulation also plays a role [3].

Local anaesthetic used:

Local anaesthetic alone is not found to have high PONV incidence but when given with phenylephrine or adrenaline PONV is increased.[3]

Resting heart rate

Patients having a resting heart rate of more than 60 beats per minute have a higher incidence of PONV as compared to patients whose heart rate is less than 60 beats per minute. Preoperative anxiety may have a role in increasing postoperative nausea and vomiting. The resulting nausea and vomiting during epidural and intrathecal block is mainly due to:

- Reduced cerebral blood flow secondary to systemic hypotension (due to vasodilatation).
- Vagal stimulation occurring during surgical procedures especially during intraabdominal, gastrointestinal manipulation as in caesarean section, hysterectomies, colon operation.
- Increased gastrointestinal peristalsis because of the preganglionic sympathetic blockade.

Compared to spinal, epidural anaesthesia has a lower incidence of PONV. Intrathecal and epidural opioids and/or local anaesthetic injection for post -operative pain relief is a common practice now. When hydrophilic opioids like morphine are being used the incidence of PONV

is higher due to rostral spreading of the drug from injection site to CTZ and vomiting centre. However, the lipid soluble drugs like fentanyl have less of rostral spread. When equipotent doses are used incidence of emesis after epidural or intrathecal injection is similar. [3]

3) Regional anaesthesia (peripheral nerve block)

Incidence of PONV after peripheral regional anaesthesia is lesser when compared with that of central neural blockade. Bonica noted that on supplementing regional anaesthesia with general anaesthesia the incidence of PONV increased to a much greater value than the combined values of the two techniques separately. [6]

4) Monitored anaesthesia care:

Many procedures can be done using just local anesthetics and intravenous analgesia sedation technique (e.g. Cataract extractions, breast biopsies, cosmetic plastic surgery, endoscopy etc.). Though there is a reduced incidence of emesis in these patients, still they are not 100% free of PONV risk[3].

F. Post-operative factors:

Pain:

Pelvic and visceral pain is a common reason for PONV. Anderson and Kronig observed that when pain was relieved most of the time this relieved the associated nausea also, which increased if naloxone reversed the opioid mediated pain relief. There is also a vestibular component, because vestibular disturbances at the time of patient movement and

during early ambulation (especially following the use of opioids) contribute to an increased incidence of PONV[2,3].

Dizziness:

PONV is higher in patients who have dizziness. This may be due to the orthostatic hypotension during central neuraxial blockade secondary to unrecognized hypovolemia. Orthostatic hypotension (secondary to dehydration due to inadequate fluid replacement), visual stimuli and psychological factors may further increase PONV. Greater vagal tone may aggravate the dizziness and nausea and may also reduce the medullary blood to CTZ. Correction of pre-existing fluid and electrolyte imbalance and also a proper perioperative intravenous hydration must be done, so that the fluid administration intra operatively and post operatively will be adequate to maintain a urine output of 0.5 ml/kg/hr [2, 3, 6].

Ambulation:

Sudden movement or changes in position or transporting of patient from the theatre to the ward may precipitate nausea and vomiting, especially in those patients who have received opioids. This is due to the sensitization of the vestibular system to motion induced nausea and vomiting. [2, 3, 6]

Oral intake:

The timing of starting the oral intake post operatively influences the chances of PONV. Martin et al found restricting the oral intake during the first 8 post-operative hours caused a significant reduction of PONV[2, 6].

RISK ASSESSMENT OF PONV[12]:

PONV is very much multifactorial. Hence many studies and researches have been conducted and analyzed with the hope of at least developing a method to assess and quantify the risk factors that increase the chances of PONV[12].

The first form of such a complete study was conducted by Palazzo and Evans in the United Kingdom who applied multiple logistic regression analysis in 148 patients undergoing minor orthopedic surgery. One year later in another study conducted by Cohen MM et al consisting of 1600 patients carried out over four centres in Canada, logistic regression was applied to the data. The importance of these studies was that they could establish the risk factors and independent predictors of PONV. However no standardization of the predictors of PONV was published. The breakthrough in this came following two studies conducted by two groups independently:

One of the studies was by Koivuranta and colleagues while another study was by Apfel and colleagues. The first of the two studies to be published was the one by Koivuranta which developed a simplified model consisting of five of the strongest predictors. They included

1. Female gender
2. Previous experience of PONV
3. Duration of operation lasting over 60 minutes
4. Previous history of motion sickness
5. Nonsmoking patients

When 0, 1,2,3,4 or 5 of these independent predictors were present the risk for PONV was:

17%, 18%, 42%, 54%, 74%, 87%

A cross validation of this study with the study conducted by Apfel proved that risk factors from one centre were able to predict the PONV from the other centre and they also found that a simplification of the existing score did not weaken the discriminating power. They then combined a simplified scoring system.

Their simplified scoring system consisted of four predictors of risk :-

i. Female gender
ii. History of previous PONV or motion sickness
iii. Nonsmoking patients
iv. Use of opioids post operatively

If zero, one, two, three or four of the risk factors were there, the incidences for PONV were 10%, 21% , 39%, 61% and 79%.

This scoring was developed for PONV prediction in inpatients. Another scoring system was developed by Chung et al for considering the outpatients. This was a more complex predictive value which included also the type of surgery for the risk factor. This was however an inferior scoring system compared to the simplified risk scores.

These models gave the prediction scores in the adult population and were not applicable to the paediatric patients. Therefore Ebehart and colleagues developed a simplified risk scoring in the children that predicted POV. They took into consideration four variables

1) Duration of surgery more than or equal to half an hour
2) Age greater than or equal to three years
3) Strabismus surgery
4) A history of previous POV or PONV in immediate family

The presence of 0, 1, 2, 3 and 4 risk factors showed a POV incidence of 9%, 10%, 30%, 55% and 70% respectively

TREATMENT OF PONV

The treatment modalities available for treatment of PONV can be broadly classified into non pharmacological and pharmacological methods

Non – pharmacological approach

1. Acupressure or acupuncture of P_6 point:

This method is used most often in the prevention of nausea in pregnancy, cancer chemotherapy and also in PONV. This is performed at the Neiguan point or P_6 which is situated between the tendons of Palmaris longus and flexor carpi radialis longus and measured at 2 Chinese inches from the distal skin crease. One Chinese inch is the width of the interphalangeal joint of the thumb (i.e. at 3 finger breadth below the crease of hand wrist)

Dundee et al investigated the effect of invasive acupuncture and P_6 acupressure (by applying 10 Hz of electrical and manual stimulus respectively) applied for 5 minutes at the time of premedication. He observed that there was a considerable reduction in the incidence of postoperative nausea and vomiting especially in the first 6 postoperative hours when compared to the controls.

P_6 acupressure was as effective as the P_6 acupuncture over the early post-operative period (that is in the first 0 to 1 hour) but it has lesser effect than the P_6 acupuncture over the 1- 6 hours of postoperative period. This method was found to be as effective as injection metoclopramide 10 mg given intravenously or injection cyclizine 50 mg given intravenously. On being compared with prochlorperazine, P_6 pressures reduced nausea but not vomiting significantly up to 1 and 2 postoperative days when compared to the placebo. The benefit of P_6 acupressure has been investigated for preventing PONV in lengthy major gynaecological surgery lasting for up to 6 – 8 hours. Preoperatively, a small metal bullet was fastened to the P_6 acupressure point by means of an elastic bandage and was kept for 24 hours postoperatively and the patients were observed. The P_6 acupressure group was observed to have significant decrease in nausea up to the 6^{th} post-operative hour when compared to placebo group.[3]

Transcutaneous acupoint stimulation (TAES also called as the relief band) is a battery powered electrical device. This stimulates the P_6 point continuously for 6-12 hours and shows promising benefits in preventing post-operative nausea and vomiting as well as chemotherapy associated nausea and vomiting. [3]

Acupressure at P_6 point and TAES is considered to be an effective alternative to conventional antiemetic therapy. However the use of acupressure though a promising treatment, it is not a long lasting remedy.

Lewis et al found that acupuncture did not relieve PONV associated with strabismus surgery in the paediatric group. Low frequency electrical stimulation is better than higher frequency in preventing PONV by stimulation of P_6 point.[3]

Ginger Root (Zingiber officianale)

For thousands of eras, herbal medications have been practiced for controlling nausea and vomiting. Ginger root had been found statistically significant in controlling post-operative nausea and vomiting in two double blinded placebo controlled study. Bone at al found statistically relevant reduction of PONV with 0.5 mg of powdered ginger root in capsule when compared with placebo in a response rate equivalent to metoclopramide [3].

Positive Encouragement

Reinforcing desirable thoughts by providing positive suggestions are used by many people to help change undesirable behavior. Eastern mystics have shown control over autonomic function such as metabolic rate and heart rate.

Two studies examined power of positive suggestion to decrease PONV.

1) Williams et al studied 60 women during major gynaecological surgery and demonstrated less nausea and vomiting in patients who received positive suggestions.
2) Lauder et al studied 266 patients and demonstrated that the women randomized into the positive suggestion group required 16.5% less of antiemetics than the control group [3]

Pharmacological Approach:

A specific PONV antiemetic management plan can be formed by a complete preanaesthesia history. Patients with obvious risks of PONV in terms of patient, surgery or anaesthesia should be assessed and those patients likely to be benefitted from prophylactic antiemetics should be identified. Also patients in whom PONV would likely compromise patient safety, delay recovery and discharge or cause a hospital admission would be benefitted from prophylactic antiemetic treatment. There are many high risks scores formulated to identify PONV[12].

Traditional antiemetic therapy:

Different classes of agents used for PONV includes anticholinergic, dopamine antagonists, antihistamines, sedatives/anxiolytics, phenothiazines, butyrophenones and a combination of these drugs.

The reason for the availability of these many agents to control PONV is due to the multifactorial origin of PONV with no single medication being a 100% solution for all patients and for all types of surgery and anaesthesia. A combination therapy approach would therefore be more beneficial to treat a patient with difficult to treat, severe and persistent PONV as their multiple emetic receptors would be inhibited[2,3].

Anticholinergic drugs:

This group belongs in the oldest class of antiemetics. They inhibit the muscarinic and cholinergic CNS emetic receptors present in the cerebral cortex and pons. The action of selective muscarinic M_3 and M_5 inhibitors prevents motion sickness. Scopolamine has an effective

preoperative antiemetic effect along with sedation. Atropine is not as potent an antiemetic as scopolamine. Both have better action against motion induced vomiting than motion induced nausea. Transdermal scopolamine is more effective against motion sickness than postoperative nausea and vomiting. Anticholinergics can be combined with opioids for premedication for prophylactic treatment of PONV. Scopolamine prevents the impulses from vestibular nuclei from reaching the higher centres in the CNS, such as the reticular activating formation and the vomiting centre. It corrects the imbalance of acetylcholine and noradrenaline in the CNS which occurs in patients with motion sickness[2, 3].

Transdermal scopolamine can prevent PONV caused by opioids (e.g. epidural morphine). It can also reduce the incidence of PONV associated with outpatient laparoscopy. But in order to be of benefit the patch needs to be applied many hours prior to induction. Transdermal scopolamine has conflicting results in preventing emesis in children with strabismus surgery. But since opioids have longer emetogenic properties than the antiemetic properties of scopolamine, delayed post -operative nausea and vomiting may occur.

The adverse effects of anticholinergic drugs include sedation, dry mouth, blurred vision, mydriasis, dysphonia, confusion, disorientation, hallucination, memory loss and urinary retention [2,3].

Phenothiazines:

They have a heterocyclic or aliphatic ring attached to the position 10 of a tricyclic nucleus. They block the dopaminergic receptors in CTZ to

bring about the antiemetic action. They are used worldwide for their antiemetic action. They include promethazine, prochlorperazine, perphenazine, chlorpromazine, etc. Aliphatic phenothiazines (promethazine, chlorpromazine) have more of sedative rather than antiemetic potency when compared to the heterocyclic phenothiazines. Phenothiazines however produce adverse effects like hypotension, sedation, lethargy during recovery and may prolong hospital stay. Phenothiazines exert a direct D_2 receptor blockade in CTZ and have a moderate anticholinergic and antihistaminic action. They can tranquilize and sedate and are particularly effective for countering the effect of certain drugs on the CTZ. They are more effective in treating PONV but less effective to treat motion sickness.

Heterocycline phenothiazines are better than aliphatic phenothiazines in preventing PONV but they also have a higher incidence of extrapyramidal symptoms like:

1) Acute dystonia (trismus, torticollis, opisthotonus, oculogyric crisis)
2) Tardive dyskinesia
3) Akathesia (motor restlessness)
4) Pseudoparkinsonism

Neuroleptic malignant syndrome has been noticed as a side effect with phenothiazines/ droperidol and metoclopramide. It is a syndrome characterized by hyperpyrexia, autonomic instability, muscle rigidity and altered mental status. Anticholinergic adverse effects of phenothiazines

are tachycardia, dry mouth, urinary retention, drowsiness and hypotension which can be treated with IV fluids and phenylephrine [2,3].

Butyrophenones

Droperidol and haloperidol have similar antiemetic effect as phenothiazines. They are alpha blockers. The adverse effects include sedation and EPS. They act on the area postrema and CTZ as strong D_2 receptor antagonists. Both haloperidol and droperidol have antiemetic properties but droperidol is used more commonly in anaesthesia. They have tranquilizing activity but haloperidol produces less sedation than prochlorperazine[2,3].

Both IM droperidol 5 mg and haloperidol 2 mg have equipotent action. Haloperidol has a faster onset of action than droperidol. But the duration of action is longer in droperidol and has a greater affinity for the D_2 receptors in CTZ than haloperidol. Also when compared to metoclopramide 10mg, placebo and droperidol 5mg, IV droperidol 1.25mg administered just before the end of anaesthesia in major gynaecological surgeries was found to be superior. It was also found beneficial in elective orthopaedic surgery for female patients.

Droperidol 5mcg /kg intravenously administered 1hour before the end of anaesthesia was found to be effective in children in the age group of 11-15 years. The i.v dose of 0.625 mg droperidol was found to be as effective as i.v dose of 1.25mg droperidol for the prevention of PONV when given immediately after intubation[3].

Repeated and high doses of haloperidol and droperidol produce EPS, anxiety, restlessness, hypotension and sedation in both elderly and young adults[3].

Antihistamines:

These include dimenhydrinate, hydroxyzine, cyclizine and diphenhydramine. They bring their action by blocking:

1) Acetylcholine in vestibular apparatus
2) H1 histamine receptors of the nucleus of the solitary tract

They are used especially in motion sickness therapy and prophylaxis and in controlling PONV after middle ear surgery. They can also be used for treating vertigo. Their side effects are sedation, blurred vision, dry mouth, urinary retention and delayed recovery. Cyclizine and hydroxyzine have sedative effects and are supplemented with opioids for premedication. Cyclizine has a lower incidence of side effects and is more effective for PONV treatment. [3]

Hydroxyzine is an anxiolytic medication having anticholinergic, antihistaminic, bronchodilatory effects in treating motion sickness, PONV and vertigo. It has duration of action of 4 to 6 hours with minimal respiratory and circulatory depression. The antisialogogue and sedative action of hydroxyzine makes it suitable for being a premedication drug along with opioids.

The barbiturates and opioids doses should be reduced by 50% or more when being given along with hydroxyzine because the CNS depressant effects will be highly potentiated. 100mg hydroxyzine IM

given after induction is more effective than droperidol 2.5mg IM in reducing PONV. [3]

Benzodiazepines:

These include diazepam, lorazepam, midazolam. They have sedative, amnestic and anxiolytic properties. They reduce anxiety and restlessness associated with anaesthesia and surgery and thereby decreases the incidence of PONV.

IV Midazolam 75 mg /kg administered after induction prevents vomiting after tonsillectomy operations in children. Lorazepam 10 mcg/kg compared to droperidol 75 mg/kg when given after inhalational induction in strabismus surgery had similar effects for controlling PONV in children[3].

Benzodiazepines as such do not have any antiemetic action on any receptors but they reduce anxiety by decreasing catecholamines release. They have amnesia producing effects which prevents recall of any memory of PONV. [2, 3]

Benzamides:

Metoclopramide and domperidone falls in this group with specific D_2 (dopamine) antagonist activity. They are unrelated to phenothiazines and are lacking in antihistaminic properties. Metoclopramide is D_2 receptor blocking agent both centrally (CTZ and area postrema) and peripherally (gastrointestinal tract). It is a gastrointestinal prokinetic drug which increases the lower oesophageal sphincter tone and increases the upper gastrointestinal tract motility. It crosses the blood brain barrier. It

has fewer side effects and does not affect the anaesthesia recovery time or the haemodynamic stability. Rapid administration may cause abdominal cramping.

Extrapyramidal tract side effects occur in less than 1 % of patients when treated chronically especially when metoclopramide 40 – 80 mg is used daily. It may also potentiate the CNS depressant action of other drugs. The EPS incidence caused by butyrophenones and phenothiazines may be enhanced by metoclopramide. This drug should be avoided in patients with history of seizure disorders and preexisting pyramidal symptoms. It is very beneficial and popular drug in treatment of radiation sickness, drug induced vomiting and migraine associated vomiting. Metoclopramide reverses gastric stasis induced by morphine. Metoclopramide 0.15 mg/kg IV given after the delivery of the baby reduces PONV in elective caesarean section under epidural anaesthesia[2,3].

After tonsillectomy, 0.15 mg/kg IV metoclopramide given on arrival in the post anaesthesia care unit prevents PONV in children. When given as a prophylactic antiemetic agent prior to induction there have been increasing doubts about its antiemetic efficacy. This may most probably be due its shorter duration of action

Domperidone is also a drug in the benzimidazole group. It is pharmacologically similar to metoclopramide but is similar in structure to haloperidol. It acts on the CTZ against its D_2 receptor. EPS is lower with domperidone as compared to metoclopramide. It cannot cross blood brain

barrier. It increases the gastric emptying time due to its prokinetic properties. It causes a better lower oesophageal sphincter tone

Domperidone is similar to metoclopramide in its effectiveness to prevent PONV but is superior to metoclopramide in treating PONV. The antiemetic treatment is dependent highly on the timing and the route of administration. A dose of intravenous domperidone 5- 10 mg given in the recovery room can be effective in treatment of postoperative emesis. Its effect is only as good as that of placebo if given preoperatively or immediately after induction.

Benzquinamide is a short acting benzoquinone derivative with antiemetic property due to its antiserotonin, antihistaminic and anticholinergic activity. It blocks these receptors in the CTZ. Sedation is a common adverse effect. It is effective when given intramuscularly for preventing and treating PONV. When administered intravenously it causes tachycardia, ventricular arrhythmias and hypertension[2, 3].

Serotonin receptor antagonists:

The (5 HT_3) receptor antagonists are highly selective and specific drugs used in control of nausea and vomiting. They are also found to be beneficial in the treatment of radiation induced nausea and vomiting and also in chemotherapy induced nausea and vomiting.

This group includes granisetron, tropisetron, dolasetron and ondansetron.

Role of $5HT_3$ receptors:

The various agents used to prevent or treat nausea and vomiting acts as dopamine, muscarinic or histaminic antagonists. Radioligand

binding studies have shown a high density of $5HT_3$ receptors in the areas involved in emetic reflex. $5HT_3$ receptors are present on the vagal terminal innervating the gastrointestinal mucosa and in the same vagal afferent nerves situated at the brainstem vomiting system (i.e. the nucleus of the solitary tract, dorsovagal nucleus and CTZ)[3].About 80% of 5HT are present in the enterochromaffin cells of the gastrointestinal mucosa. This is released during radiation or by cytotoxic drugs where being close to the vagal afferents, they activate these nerve endings and leads to stimulation of the emetic reflex. Large amounts of 5HT are located in the gastrointestinal mucosa at its enterochromaffin cells. It gets released due to radiation or cytotoxic drugs and being close to the vagal efferents, it can activate them to initiate the vomiting reflex.

The action of 5HT includes provocation of pain, contraction and relaxation of the smooth muscle present in the blood vessels and of the ones present in airways and the gastrointestinal tract. It has got platelet aggregation activity and reflex actions on the heart. Serotoninergic pathways have been implicated for many actions in the CNS such as induction of sleep, influencing aggression, depression, anxiety and for eating behavior. They also have a role in migraine induced emesis.

Over the past two decades, greater interest has been placed on the role of 5HT because of their highly selective actions on 5HT receptor subtypes. They are divided in 7 main groups ($5HT_1$ to $5HT_7$), the $5HT_1$ and $5HT_2$ receptors have further subtypes.

Ondansetron: this was the first of the approved drug for PONV and it could be administered both intravenously and orally. They were found equally useful in both adults and children. The effective dose was found to be 4mg given intravenously at the start of anaesthesia or 8 mg given orally 1-2 hours before the induction. In children older than 2 years and with weight less than 40 kg, 0.1 mg/kg IV is recommended.

Tropisetron: It is a highly selective and potent $5HT_3$ antagonist. It is also a weak $5HT_4$ antagonist. It has also been tried for the treatment of migraine, carcinoid syndrome and ventricular arrhythmias. Headache is one major side effect while constipation, fatigue and diarrhea pose to be a minor side effect. Also transient variation in blood pressure has been reported. In most of the studies considering tropisetron for PONV prevention, it was found that tropisetron is more efficacious than placebo. Tropisetron 5 mg IV given as premedication is found to be effective in PONV prevention after gynaecological and breast surgery. IV tropisetron 2 mg was determined to be the optimal effective dose for treatment of PONV during a variety of non- abdominal and abdominal surgeries in a study by Alon et al [(3)].

Dolasetron: This drug gets converted to its more active form hydrodolasetron by the action of the plasma enzyme called carbonyl reductase. This drug is 100 times more potent than ondansetron. Its contradiction is AV block 2 or 3 and/ or concomitant therapy with class 1 or 3 antiarrhythmics. For the prophylaxis and treatment of PONV 12.5 mg IV is used in adults which is to be given 15 to 30 minutes towards the end

of anaesthesia. Dolasetron given 1 – 2 hours prior to anaesthesia in children through oral route had similar pharmacokinetic effects as that of IV preparation given at induction. It has increased clearance, with a shorter half-life in children when compared with healthy young adult volunteers.

Nontraditional antiemetic therapy:

Ephedrine:

0.5 mg/ kg ephedrine given intramuscularly had similar effectiveness to that of 0.04 mg/ kg of droperidol in preventing PONV when considering the outpatients of gynaecological laparoscopy procedures and it also had significantly greater efficiency than placebo. It did not show any effect on BP nor did it have any sedative adverse effects. It also had similar antiemetic effectiveness in prevention of PONV in other laparoscopic cases with no hemodynamic variations. Ephedrine 0.5mg/kg given intramuscularly had similar effectives to that of Propofol 0.25mg /kg given intravenously. Intramuscular ephedrine is particularly useful antiemetic for PONV when it is related to orthostatic hypotension and or fluid dehydration. [3]

Propofol:

The exact mechanism of antiemetic activity of propofol is not determined. But the use of intraoperative Propofol given intravenously was found to be as effective as that of intravenously given 4 mg Ondansetron in preventing PONV especially upto 6 hours of post-operative period. Subhypnotic dose of intravenous thiopentone (1 mg/kg)

was found to be less effective than subhypnotic doses of propofol (0.05 mg/kg) in preventing PONV for middle ear surgery especially during the first 6 hours of post-operative period. Also the subhypnotic dose of propofol was superior in preventing PONV associated with sevoflurane anaesthesia than desflurane anaesthesia during outpatient laparoscopic cholecystectomy. The incidence of PONV had an overall reduction when 0.1 ml/kg/hr infusion of i.v propofol was used over a 20 hour postoperative period in comparison to 10% intralipid placebo control [(3)].

Corticosteroids:

These were first used in preventing chemotherapy induced nausea and vomiting. Their effectiveness in PONV is probably associated to their anti-inflammatory and / or membrane stabilizing action. 1mg/kg of intravenous dexamethasone could be used intravenously to reduce PONV in children of 2 – 12 years during tonsillectomy, when administered before the start of surgery after mask inhalational induction (when compared to placebo) [(3)].

Inhaled isopropyl alcohol:

This has been suggested as a potential antiemetic for treating established PONV. Merith et al observed inhaling isopropyl alcohol was as effective as other standard antiemetic drugs in rescue treatment of PONV[(3)].

Neurokinin – 1 antagonists:

These are unique compounds .They include CP - 122, 21; L – 754030, GR – 205171, MK – 869, CJ11, 974.

Their mechanism of action seems to be associated to the inhibition of substance P in emesis associated regions in brainstem. They are particularly helpful in treatment of delayed emesis associated with cancer therapy, lower abdominal procedures and major gynaecological procedures[3].

PHARMACOLOGY OF THE DRUGS IN THE STUDY

PHARMACOLOGY OF METOCLOPRAMIDE[13,14]

Metoclopramide:

This drug was introduced in the early 1970 as a gastric hurrying drug and is now used worldwide as an antiemetic drug. It is a dopaminergic receptor antagonist and is also a prokinetic drug.

Metoclopramide hydrochloride is a crystalline and white substance. It is odourless and freely soluble in water. Chemically it is known as 4-amino-5-chloro-N-[2-(diethylamino)ethyl]-2-methoxy benzamide monohydrochloride monohydrate and has the following structural formula:

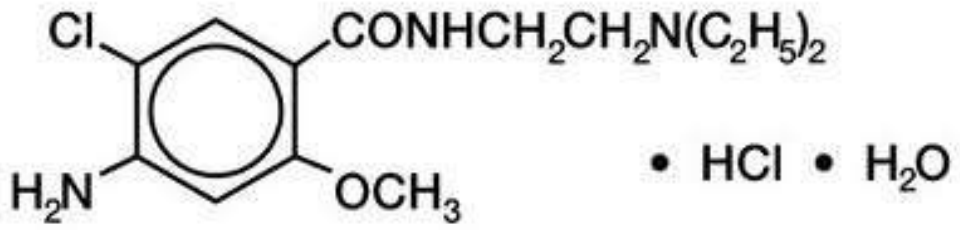

Fig.1 – Structure of Metoclopramide

It has a pH of 2.5 – 6.5 for IV or IM injection and has a molecular weight of 354.3. Metoclopramide hydrochloride 10.5 is equivalent to 10 mg anhydrous substance and 8.9 mg of anhydrous base. It is water soluble.

Presentation: It is available as a clear, colourless solution in 1 ml ampoule containing 5 mg/ml of Metoclopramide hydrochloride. It is also available as 10 mg tablets 15/30 mg slow release capsules and as a syrup containing 1 mg/ml.

Mechanism of action: Metoclopramide is a prokinetic drug. Metoclopramide sensitizes tissues to the action of acetylcholine. It increases the gastric emptying and intestinal transits by increasing the tone and amplitude of gastric contraction. It also increases the peristalsis in the duodenum and jejunum and at the same time relaxes the pyloric sphincter. The lower oesophageal sphincter pressure is increased due to its actions. There is also a direct action on smooth muscle to increase its tone.

The drug's antiemetic effects are due to peripheral and central dopaminergic (D_2) blockade. This increases the vomiting threshold at CTZ. It also decreases the sensitivity of the visceral afferents which supply information to vomiting centre.

The onset of pharmacological action with intravenous administration takes 1 – 3 minutes and with intramuscular action it takes 10 – 15 minutes while it takes 30 – 60 minutes after oral administration.

Pharmacokinetics:

Absorption: it has a rapid and almost complete absorption from the gut. However it undergoes hepatic first pass metabolism and has a wide range of bioavailability of 32 – 97%.

Distribution: It has a large volume of distribution of about 2.2 – 3.5 L/kg. Metoclopramide is 13 – 22% protein bound.

Metabolism: It is metabolized primarily in the liver. The major metabolite is a sulphate derivative.

Excretion: 80% of the drug gets excreted in urine within 24 hours. 20% of the drug remains unchanged and the remainder is conjugated as sulphate and glucuronide metabolite. It has an elimination half-life of 2.6 – 5 hours with a clearance of 8.8 – 11.6 ml/min/kg. Renal impairment affects the clearance of Metoclopramide as shown in a study of patients with varying degrees of renal impairment where a reduction in creatinine clearance was correlated with a reduction in plasma clearance, renal clearance, non-renal clearance and increase in elimination half-life.

Pharmacodynamics:

CVS: it causes occasional hypotension during general anaesthesia, dysrhythmias, cardiac arrest and hypertension in patients with pheochromocytoma.

CNS: it raises the vomiting threshold at CTZ. It has neuroleptic effects including antipsychotic action due to its central dopaminergic antagonist action.

Alimentary System:

It increases the lower oesophageal sphincter pressure to almost 17 mmHg and increases gastric emptying time and gastric contractions. It also increases the small intestinal transit time. It has no effect on gastric secretion.

Genitourinary System: The drug increases ureteric peristaltic activity.

Metabolic effects: Metoclopramide increases prolactin release and transiently increases aldosterone secretion.

Uses:

1) Nausea and vomiting induced by general anaesthetic agents, cytotoxic agents and radiotherapy or by biliary and hepatic disorders.
2) In digestive disorders like hiatus hernia, reflux oesophagitis and gastritis.
3) Diagnostic radiological examination of gastrointestinal system to increase the gastric emptying where delayed emptying interferes with radiological examination of gastrointestinal system.
4) Migraine
5) Post-operative gastric hypotonia

Adverse Effects:

- It can cause extra pyramidal side effects like tardive dyskinesia, acute dystonic reactions. The extrapyramidal effects occur more often with higher doses in elderly and in people with renal failure.
- It can also cause neuroleptic malignant syndrome.
- It can also cause Parkinsonism like symptoms.
- It also increases prolactin secretion.
- Dizziness, headache, drowsiness, bowel upset, urinary incontinence is common.

- Depression, hypertension, hypersensitivity reactions and blood disorders are common side effects.

Contraindications:

1) Metoclopramide is not to be used in conditions where stimulation of gastrointestinal motility can be dangerous, such as in mechanical obstruction, gastrointestinal hemorrhage or perforation.
2) It should not be used in patients with pheochromocytoma also because the drug can cause a hypertensive crisis, by the release of catecholamines from the tumor.
3) It is contraindicated in subjects with known sensitivity to the drug.
4) It should not be used in epileptics and patients receiving other drugs which can cause extrapyramidal reactions, because the severity of the extrapyramidal reactions can get increased.

Routes of Administration/Dosage:

Metoclopramide can be given orally, intravenously or intramuscularly. By all routes the dosage is 10 mg 8 hourly. A dose of 1 – 2 mg/kg is used in cisplatin associated nausea and vomiting.

PHARMACOLOGY OF RANITIDINE[13,14]

Ranitidine is a H2 (Histamine) Receptor blocker, which is chemically N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, HCl. It has the following structure:

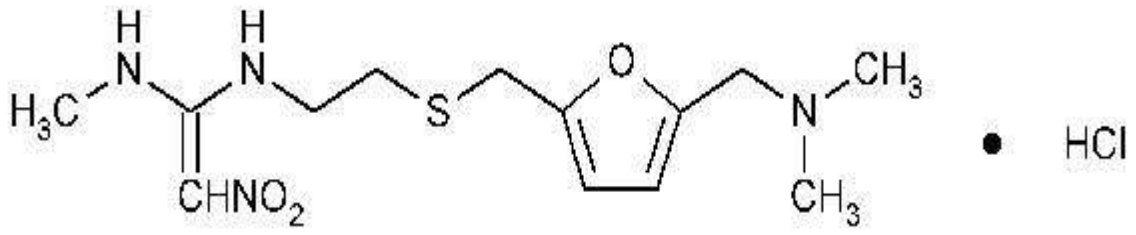

Fig.2 - Structure of Ranitidine

The empirical formula is C13H22N4O3S·HCl, having a molecular weight of 350.87.

It appears as a white to pale yellow, granular substance and is soluble in water. It has a sulphur like odour and has a bitter taste.

Mechanism of action:

Ranitidine acts as a competitive histaminergic H_2 receptor blocker which blocks histamine action necessary to bring about the action of gastrin and acetylcholine in the gastric parietal cell.

Presentation:

It is present as a clear solution for IM or IV injection containing 25 mg/ml. 150/300 mg tablets are also available. A syrup of 15 mg/ml is also available.

Pharmacokinetics:

Absorption: Ranitidine Tablets have 50% absorption after oral administration compared to an IV injection with mean peak levels of 440 to 545 kg/ml. Food and antacids do not alter absorption.

Distribution: It has a volume of distribution of about 1.4 L/kg. 15% of the drug is protein bound.

Metabolism: It is metabolized in liver by oxidation and methylation. Liver dysfunction does not significantly affect Ranitidine half-life, distribution, clearance and bioavailability.

Excretion: The principle route of excretion is urine. It has a clearance of 10 ml/min/kg and has an elimination half-life of 1.6 – 2.5 hours. In a study, four patients with clinically significant renal dysfunction administered IV Ranitidine 5 mg showed a plasma half-life of 4- hours with a clearance of 29 ml/min and a volume of distribution of 1.76 L/kg.

Pharmacodynamics:

The drug's major action is in the alimentary system where it has an anti-secretory action and reduces the gastric acid secretion, its volume, and also reduces hydrogen ion and total pepsin content.

They have no action in the cardiovascular or respiratory centre. The drug does not have any anti-dopaminergic or anti-androgenic actions that are associated with cimetidine. The drug crosses the placenta but no adverse effect on fetal well-being is noticed.

Uses:

1) Reflux oesophagitis
2) Zollinger – Ellison Syndrome
3) Peptic ulcer disease
4) In critically ill patients to prevent stress ulceration
5) Prior to general anaesthesia to reduce the risk of acid aspiration

Contraindications:

It is contraindicated in patients with hypersensitivity to the drug.

Adverse Reactions:

The adverse reactions associated with Ranitidine are rare manifestations in the following systems.

CNS: Rarely malaise, dizziness, insomnia, vertigo, somnolence, mental confusion/ depression/ hallucinations are seen in severely ill elderly patients. Blurring of vision and rare involuntary motor disturbances are seen.

Cardiovascular: they can rarely cause arrhythmias.

Gastrointestinal: Constipation/ diarrhea, abdominal discomfort/ pain, rare reports of pancreatitis

Hepatic: Rarely, they can cause alteration of liver function tests

Hematologic: Thrombocytopenia, leucopenia and granulocytopenia are seen in few patients.

Endocrine: No significant endocrine activity is induced by ranitidine . Cases of galactorrhoea and gynaecomastia have been reported both in males and females. Anaphylactoid reactions may occur

Respiratory: In a large epidemiological study, there has been shown an increased risk for development of pneumonia in H_2 – receptor blockers with a relative risk of 1.63, however no causal relationship has been established.

Routes of administration/ dosage:

Ranitidine may be administered as slow IV or IM, with dose being 50 mg 6 – 8 hourly. Oral dose of 150 mg twice daily can be given.

PHARMACOLOGY OF ONDANSETRON[13,14]

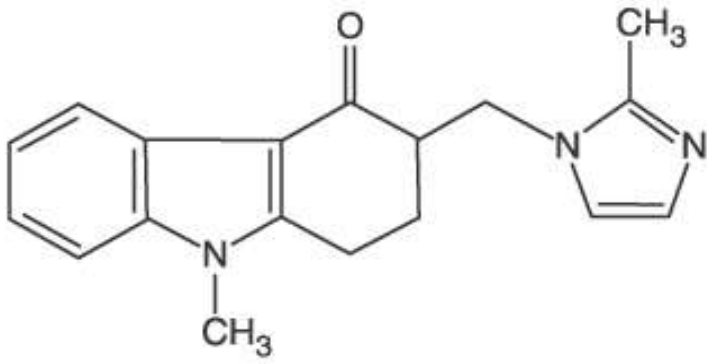

Fig.3 – Structure of Ondansetron

Ondansetron is a selective 5 - HT_3 blocker. 5 - HT_3 is present in high density in the area postrema and in the nucleus tractus solitarius.

Chemically it is 1, 2, 3, 9-tetrahydro-9-methyl-3-[(2-methyl-1 H-imidazol- 1-yl) methyl]-4H-carbazol-4-one. The structural formula is C18H19N3O is the molecular formula and it has a molecular weight of 293.4.Intravenous drug contains an isotonic aqueous solution which contains ondansetron hydrochloride dehydrate 2mg/ml. It has a pH of 3.5.It contains citric acid monohydrate and a sodium citrate and has a shelf life of 3 years

Presentation:

It is present as a colourless, clear solution in 2/4 ml ampoules which contains 2 mg/ml ondansetron hydrochloride dihydrate. It is also present as 4/8 mg tablets.

Mechanism of action:

Ondansetron is a highly selective antagonist of $5HT_3$ receptor. It has both central and peripheral action. On having emetogenic stimuli 5 –

HT_3 is released in the small intestine from the enterochromaffin cells which brings about the vomiting reflex by action of vagal afferents via the 5- HT_3 receptors. Ondansetron blocks this reflex. Vagal afferents may also cause release of 5- HT_3 in area postrema.

Pharmacokinetics: -

Absorption:

Ondansetron can be absorbed well from the gut. It has a bioavailability of 56 -60%.Bioavailability is slightly enhanced in the presence of food but not by antacids.

Distribution:

The drug is 70 – 76% protein bound. The volume of distribution is about 2L/kg.

Metabolism:

The drug is metabolized in the liver by either hydroxylation or by N– demethylation of the indole ring and is followed by conjugation with glucuronic acid or sulphate.

Excretion:

Less than 5% is excreted in the urine unchanged. The clearance of the drug is 6.3 ml/min/kg. The elimination half-life is 3 hours. However there is reduction of clearance and increased elimination half-life in the elderly but no dose adjustment is recommended for the elderly. In hepatic impairment, the clearance is reduced 2 fold and the half-life is increased to 11.6 hours. Therefore, the dose should be limited to 8 mg/day. There is

no requirement for dose adjustment in renal impairment. Clearance is also increased in children.

Pharmacodynamics:

CVS: The drug has no effect on the cardiovascular systems.

RS: The drug does not have any effect on the ventilation.

CNS: Ondansetron is free of sedative side effects on the CNS and does not impair performance of psychomotor tests.

GI System: The drug has no antimotility activity in the gastric system, but it increases the large bowel transit time.

Uses of Ondansetron:

1) McKenzie R et al in 1993 have established ondansetron as effective antiemetic for preventing PONV or treating established PONV.
2) In chemotherapy induced nausea and vomiting. The chemotherapeutic agents cause nausea and vomiting which is especially high with cisplatin therapy. Ondansetron is particularly effective and can be used as 8 mg and up to 10 mg in treating chemotherapy induced nausea and vomiting. Studies have shown improved effectiveness with addition of 20mg IV dexamethasone.
3) Radiotherapy: In radiotherapy, irradiation of the entire body, in particular the upper abdomen is a cause of emesis. Ondansetron 8mg is efficient in reducing emesis in such scenarios.
4) Use in Anaesthesia: Several studies compared Ondansetron with placebo in patients undergoing surgery and anaesthesia and showed that ondansetron group suffered less PONV compared to placebo

group .The recommended dose for preventing PONV is 8 mg orally one hour prior to surgery. This can be followed by 2 doses of 8 mg at 8 hourly intervals.

Contraindications

The use of apomorphine with ondansetron is contraindicated as this combination can cause profound hypotension and loss of consciousness. It is also contraindicated for patients known to have hypersensitivity to the drug.

Side Effects:

Ondansetron is a well-tolerated drug with only mild and transient adverse reactions which includes headache, dizziness, abdominal discomfort and constipation. Rarely, ondansetron may cause hypersensitivity reactions. Only one study reported the incidence of gastrointestinal stasis. Disturbances in liver functions as seen by elevated liver enzymes have been reported. These disturbances are however self-limiting. Ondansetron may lead to an increase in arterial pressure with a reflex decrease in heart rate. But however studies have shown that there are no significant changes in the heart rate or in the systolic or diastolic pressure. There is no effect on ventilation frequency or oxygen saturation. There is no impairment of psychomotor function. It has no antagonism of dopamine receptors and therefore is free from the extrapyramidal symptoms caused by metoclopramide.

Routes of administration.

It can be given as 8 mg orally at 8 hourly intervals or as a single dose of 4 mg intramuscularly or intravenously.

Review of Clinical Studies:

The ever required need to understand, prevent and treat PONV is reflected by the presence of a large number of literatures on PONV. At least 2000 randomized controlled trials are published to date and almost 200 new studies are being published every year[12].

In recent large studies the incidence of PONV is (20-30)%[2,3].While in laparoscopic procedures the incidence is (53-72%)[4].In a study[15] which collected and analyzed data over a period of three years to evaluate the incidence and severity of anaesthetic complications following pediatric ambulatory surgery in 4998 patients it was reported that 33% of overnight admissions were due to PONV. Many drugs are hence frequently studied and reported.

In a systematic review and meta-analysis conducted by Mishriky et al[16] metoclopramide was studied for its efficacy and prophylaxis in nausea and vomiting during and after caesarean delivery. They conducted a literature search of Cochrane Central Register of Controlled Trials, MEDLINE (1966-2011), EMBASE (1947-2011), CINAHL and Google scholar and studied RCTs which compared metoclopramide to placebo, used in women having caesarean delivery under neuraxial aneasthesia.11 studies involving 702 patients were studied. Administration of 10mg

metoclopramide resulted in significant reduction of intraoperative nausea and vomiting and also early PONV. EPS were not reported in any patients.

De Oliveira[17] et al did another meta-analysis to prove the efficacy of metoclopramide to prevent PONV following general anaesthesia. This study questioned the earlier study by Yoshitaka Fuji[37] which had reported that 10mg systemic metoclopramide is not effective to prevent PONV in patients undergoing general anaesthesia. A worldwide search for RCT which evaluated the use of 10mg metoclopramide for PONV was carried out and 30 trials involving 3328 subjects were evaluated. They proved that metoclopramide reduced the incidence of PONV over 24 hours when compared with control, with an odds ratio of 0.58 and number needed to treat 78. When considered as separate outcome metoclopramide reduced the 24 hour nausea (with OR of 0.51 and number needed to treat =7.1) and also 24hour vomiting (with OR of 0.51 and number needed to treat =83).They concluded that 10mg metoclopramide is efficient in controlling PONV.

Metoclopramide has been used for almost 50 years to prevent PONV. In a quantitative systemic review of randomized placebo controlled study Henzi et al [18] studied the use of metoclopramide in the prevention of PONV. They analyzed the data found in 66 studies with 3260 patients receiving 18 different regimes of metoclopramide and 3006 controls receiving placebo or no treatment. The best documented regimen was 10mg I.V. while in children the best documented regimen was 0.25mg/kg. Relevant end points studied were prevention of early PONV(6

Hours post- surgery) and late PONV (48 hours post -surgery) and adverse effects . The study concluded that there was no significant anti-nausea effect. The numbers needed to treat and prevent early vomiting was 5.8 (3.9-11).The drug did not have late anti-vomiting effect. Only one patient experienced extrapyramidal symptoms with metoclopramide.

William Pond[19] in a short study consisting of 50 ASA 1 and 2 women undergoing laparoscopic procedures analyzed the commonly ordered combination of ranitidine and metoclopramide which is given as premedication. The study was conducted to analyze the effect of this combination on gastric volume and pH. Here they administered Tab Ranitidine 150mg and Tab metoclopramide 10mg before the night of the surgery. Though the study was initially conducted to study only the effect of ranitidine and metoclopramide on the gastric pH and volume, the study found an interesting finding that this combination led to not only minimal degree of post-anaesthetic nausea (On an average of less than 1 in a scale of 1 to 10), but also the vomiting incidence was reduced. However they suggested that this may be due to a central antiemetic action of metoclopramide and, or a very low gastric volume. They suggested that a larger study would be necessary to produce a statistically significant result to prove the validity of the finding.

In another study conducted by Manchikanti et al[20] as early as 1984, they studied ranitidine and metoclopramide and its prophylactic effect on aspiration pneumonitis in elective surgery. They compared 10 groups consisting of 15 subjects each. Groups 1 were taken as controls

while the rest 9 groups were allotted in various regimes consisting of either ranitidine or metoclopramide alone or in combination. They found out that ranitidine and metoclopramide independently or in combination reduced the rate of aspiration pneumonitis but however no association was brought about to the effect of drug regimes in prevention of PONV.

In a comparison study conducted by Cozanitis D et al [21] the effect of ranitidine, droperidol or placebo in the prevention of nausea and vomiting after hysterectomy was studied. In this study 3 groups consisting of 60 patients were studied in a double blinded randomized manner. In the group 1, tab ranitidine was given the night before and also in the following morning one hour before the induction of anaesthesia. Thirty minutes before surgery ended they were given 0.3ml I.V. isotonic saline. The second group had placebo instead of ranitidine while before the end of operation, droperidol 0.75mg was given. The third group received only the placebo rather than the study drugs both prior to induction and before the end of surgery. The patients were monitored in the immediate postoperative period (2hours) in the recovery room and they were evaluated in the ward until the next morning. The results showed that the patients who received antiemetics had less of PONV as compared to those who didn't. With recovery room P=0.0109 and ward P=0.007, droperidol had a better effect on PONV in the recovery room (P=0.005) and there was no statistical significance with placebo and ranitidine. In the ward both the drugs were more effective than placebo (ranitidine P=0.01 and droperidol P=0.003).Rescue drug requirement was not significant in any

group. And in conclusion they had reported that both the antiemetics lead to a decrease in PONV in comparison to the placebo. However droperidol was superior to ranitidine during the immediate postoperative period.

The study by Doenicke Aw et al [22] analyzed premedication by H_1 and H_2 blockers to reduce the incidence of PONV. The background to do this study was the ever existing controversy whether the pretreatment with H_1 and H_2 had any effect in the incidence of PONV. They did a randomized prospective placebo controlled clinical study in 1194 patients undergoing surgery. The patients were assigned into the treatment group and the control group. Group 1 (n=335) received 0.1mg/kg dimentidine I.V plus 5mg/kg cimetidine I.V. ,group II (n=337) received 1.25mg/kg ranitidine plus 0.1mg/kg dimentidine I.V. Group III (n=316) received 300mg ranitidine per orally plus 0.1mg /kg dimentidine I.V. Group I.V was control group (n<=316) received 20ml saline I.V. Groups I,II,III were taken up for regional or general anaesthesia and group IV was taken for general anaesthesia. The incidence of PONV was 8.5%, 6.8% and 5.4% in groups I, II and III who had general anaesthesia. In patients who had regional anaesthesia (n=443) the incidence of nausea and vomiting was 2.5% and 1.1% respectively. However in control levels (n=161) the incidence was 28.3% for nausea and 27.5% for vomiting. They concluded that premedication with H_1 and H_2 blocking agents significantly reduced the incidence of PONV.

Nozaki et al[23] also did a study to evaluate if preoperative administration of H_2 blockers could reduce the incidence of postoperative

nausea and vomiting. They studied 80 patients undergoing elective surgeries who were randomly assigned into 2 groups with one group being the control C and the other F ,who were given the H_2 blocker famotidine 20mg I.V, 20 minutes prior to induction of general anaesthesia. The frequency and extent of vomiting was observed by monitoring and interviewing the patients at 0-6 and 6-12 hours. They found the preoperative administration of H_2 blockers tend to reduce PONV in women.

Dinesh Thakur et al[24] did a study on using the combination of metoclopramide and glycopyrrolate on patients undergoing cesarean section under spinal anaesthesia. Their objective was to study the combined effect of two frequently used traditional antiemetic drugs (metoclopramide and glycopyrrolate) and to compare it against published data of efficacy of single antiemetic drug usage in prevention of PONV in women undergoing caesarean section under spinal anaesthesia. They took seventy eight full term parturient women posted for cesarean section under spinal anaesthesia for their study. Metoclopramide 10mg & glycopyrrolate 0.2mg was given intravenously at the time of abdominal incision. The frequency of nausea and vomiting were noted. They found 3.84% incidence of nausea during operative and postoperative period. There was no incidence of vomiting. No adverse effects were observed during the study. They concluded that incidence of vomiting was low (zero case) in their study group and then they compared their data to other groups, for which the data was taken from other published research which

considered either metoclopramide, glycopyrrolate or ondansetron. They found that the differences were statistically insignificant between the groups, but however there was upper class interval limit of Z value falling above the level of significance (>1.96) in all groups which suggested that it might be significant and there is the need of further studies to prove or disprove significantly lower incidences of nausea and vomiting when combination of two drugs (glycopyrrolate plus metoclopramide) was used as the prophylactic antiemetic in elective cesarean section under spinal anaesthesia.

In a study by Leeser et al[25] the $5HT_3$ antagonists were analyzed in a randomized double blind placebo controlled study where 84 patients undergoing gynaecological operations under general anaesthesia were considered. Equal number patients in each group received either 16mg oral ondansetron or placebo. During the first hour after recovery the group given placebo had 52% and 40% of nausea and vomiting respectively and in the ondansetron group nausea and vomiting was 17% and 12% respectively. After 24hours, incidence of nausea and vomiting was 67% and 60% in the placebo group while it was only 29% and 26%in the ondansetron group. They thus concluded that ondansetron is effective in controlling postoperative nausea and vomiting.

In a randomized placebo controlled double blind study conducted by Aboulwiah et al[26] they evaluated the effect of ondansetron on nausea and vomiting during elective caesarean section under spinal anaesthesia. They

concluded that the intraoperative administration of 4mg of ondansetron significantly reduced the incidence of postoperative nausea and vomiting.

Sarkar M et al[27] in a comparative study analyzed the effect of a single dose of ondansetron to that of a single dose of metoclopramide in postoperative nausea and vomiting. They carried out a prospective randomized control study in 60 ASA grade I and II patients undergoing obstetrical laparoscopic surgery under general anaesthesia. The patients were monitored over a 24 hour postoperative period with the aim to investigate (1) the nausea and vomiting incidence, (2) efficacy of a single dose of ondansetron 4mgI.V. to a single dose of metoclopramide 10mg I.V. and (3) their side effects. The early antiemetic efficacy after 1,4,12 hours was 3.66,10 and 3.33%. respectively in the ondansetron group. There was no further vomiting after 24 hours. While the abolishing of vomiting after 1,4,12 and 24 hours was 20,20,16.66 and 3.33% respectively in the metoclopramide group when compared to the placebo group ($P<0.001$) .Their overall conclusion was ondansetron was a more effective antiemetic than metoclopramide.

Polati et al[28] studied ondansetron versus metoclopramide in controlling PONV. They studied 175 patients with PONV during recovery period from anaesthesia for laparoscopic procedure. The groups consisted of patients given ondansetron 4mg (58 patients) and placebo (60 patients).The abolishing of vomiting within 10 minutes and nausea within 30 minutes from the administration of study drugs with no further vomiting and nausea episodes during the first hour was obtained in 93.1%

of ondansetron group, 67.1% of metoclopramide group and 35% of placebo group. According to the Kaplan Meir method the probability of reducing PONV for 48 hour was 0.59 (95% confidence interval 0.45-0.71) in the ondansetron, 0.45 (0.29-0.60) in the metoclopramide group and 0.33(0.15-0.53) in the placebo group(P=0.003).They concluded that ondansetron 4mg to be more effective than metoclopramide 10mg.

Priestman et al[29] compared efficacy of ondansetron versus metoclopramide in the prevention of nausea and vomiting following high dose upper abdominal irradiation. They compared oral ondansetron 8mg TDS (in 38 patients) and oral metoclopramide 10mg TDS (in 44 patients) in preventing nausea and vomiting after single exposure of radiotherapy to the upper abdomen. On the first post irradiation day vomiting or retching was prevented in all but one patient in the ondansetron group whereas metoclopramide controlled these symptoms only in 46.1% (P<0.001). Similarly nausea was better controlled in Ondansetron. In 92-100% of the patients ondansetron was an effective antiemetic during the five days of the study period. Metoclopramide group had a range of 70% on day 1 and 95% on day 5.

Vishal Gupta et al[30] studied ondansetron, granisetron and metoclopramide for its efficacy in PONV in 60 patients belonging to ASA 1 and 2 undergoing laparoscopic cholecystectomy under general anaesthesia. They were divided into 3 equal groups (n=20).Emetic episodes in the first 24 hours were recorded. In the early post-operative period of 1-12 hours patients receiving granisetron had superior effect to

both ondansetron and metoclopramide. However after 12 hours emesis free periods were statistically insignificant between granisetron and ondansetron while metoclopramide group had no antiemetic effect.

Kaasa et al [31] compared ondansetron with metoclopramide in controlling chemotherapy induced nausea and vomiting. Antiemetic protection in 24 hours following chemotherapy was achieved in 65% (26 out of 40) in the ondansetron group and only 41% (17 out of 42 patients) in the metoclopramide group.

Sandhu T et al [32] in a prospective double blind study of eighty patients, studied the effects of ondansetron and metoclopramide in preventing PONV after laparoscopic cholecystectomy. The patients were divided into groups of forty each with one of the group randomized to receive 4mg ondansetron while the other received 10mg metoclopramide I.V towards the end of the surgery. The incidence of nausea was 45% for metoclopramide and 20% for ondansetron in the first 24 hours and this was statistically insignificant. There was no significant statistical difference between the two groups for nausea during the first 2 and 4 hours but was significant between the 4 and 2hours ($p=0.02$) . The incidence of vomiting was 20% for metoclopramide and 2.5% for ondansetron which was statistically significant. ($p=0.02$).

In another study prophylactic ondansetron versus metoclopramide for prevention of postoperative nausea and vomiting in elective caesarean section under spinal anaesthesia was studied by Sanjul Dandona et al[33]. They did a prospective, randomized, double-blind, control study of 100

women undergoing elective lower segment caesarean section. They were divided into 2 groups of 50 each with group I receiving Metoclopramide 10 mg I.V and Group-II receiving Ondansetron 4 mg I.V. Either of the drug was given to the patient as per the randomization 3-5 minutes before subarachnoid block. The patients were monitored for 24 hours postoperatively. Nausea, retching and emesis episodes were tabulated. The results indicated that both the drugs were effective in controlling the incidence of nausea in 1 hour, 4 hours and 12hours. However ondansetron was found more effective than metoclopramide for control of nausea, ($P < 0.05$). Ondansetron was also more effective in controlling the incidence of vomiting by applying ($P<0.005$).Two patients complained of headache, no rescue medication or no treatment failure was observed in ondansetron group. In metoclopramide group, two patients complained of giddiness (6%) and one complained of drowsiness (3%).

A study was conducted by Usha et al[34] with the aim to qualitatively compare the efficacy of metoclopramide, ondansetron and granisetron when used alone and when used in combination with dexamethasone in the prevention of postoperative nausea and vomiting in patients undergoing day care laparoscopic gynaecological surgery under general anaesthesia. For this study 180 adult female patients under ASA Grade 1 and 2 and aged 18 to 55 years were included. The study was done with six groups consisting of randomly selected 30 patients in each. The antiemetic drugs of the study were given intravenously. Just before induction of general anaesthesia, metoclopramide (10 mg), ondansetron

(4mg) and granisetron (3 mg) were given alone respectively in group A, B and C and in the group D, E and F these drugs were combined respectively with dexamethasone (8 mg). It was found that metoclopramide was very poor because it had only 36.7% success rate in the prevention of PONV and also had of higher incidence of side effects. The success rate in the prevention of PONV was found to be poor in ondansetron & granisetron group (63.3% & 66.7% respectively). The success rate was found to be good (nearly three-fourth, 73.3%) considering the combination of metoclopramide with dexamethasone and very good when considering combination of ondansetron and granisetron each with dexamethasone (90% in both).

A study was designed by Kulsoom Farhat et al[35] to compare the antiemetic efficacy and relative safety of intravenous ondansetron and metoclopramide for prevention of postoperative nausea and vomiting in adult female patients after elective laparoscopic cholecystectomy under general anaesthesia .This was a prospective, randomized, double-blinded placebo-controlled study . 150 adult ASA Grade I or II female patients, aged 18-55 years, undergoing elective laparoscopic cholecystectomy under GA were included in the study. Using random numbers table the patients were divided into two groups. Group A (n=50) was given ondansetron 4 mg/2ml while group B (n=50) was given metoclopramide 10 mg/2 ml intravenously just prior to induction of anaesthesia. Patients were monitored for the initial 24 hours after anaesthesia. Assessment of the presence or absence of nausea and vomiting (by simply yes or no) was

carried out by a resident anesthetist double blind to the study. The rescue antiemetic used was (cyclizine 10 mg) I/V. It was observed that compared to the metoclopramide group, the frequency of nausea and vomiting was clinically and statistically lower in the ondansetron group (p=0.035). It was also observed that the use of rescue antiemetic was significantly greater in the metoclopramide group (p=0.022).In conclusion this study showed that the prophylactic use of ondansetron was more effective and was associated with fewer side effects in comparison to metoclopramide. Moreover, the use of metoclopramide was associated with greater adverse effects, like dizziness and extrapyramidal symptoms.

Nisar et al[36] conducted a study to analyze the efficacy of ondansetron and dexamethasone in the prevention of PONV in patients undergoing laparoscopic cholecystectomy. The sample size was acquired by purposive non probability sampling. All the patients received a combination of ondansetron 4mg and dexamethasone 8mg intravenously at the commencement of surgery as prophylactic antiemetic. Postoperatively the patients were monitored for frequency of nausea and vomiting .It was observed that during the postoperative period of 24 hours, 57 (85%) patients did not experience nausea or vomiting. 10 (15%) patients experienced some degree of nausea and vomiting and required the use of a rescue antiemetic. No significant adverse effects were observed. It was concluded that the combination of ondansetron and dexamethasone given prophylactically successfully prevented nausea and vomiting during the postoperative period after laparoscopic cholecystectomy.

Fujji Y et al[37] compared the efficacy of granisetron, metoclopramide and placebo for their comparative efficacy in controlling PONV. Sixty patients undergoing general anaesthesia for major gynecological procedures were randomly selected and divided into three groups of 20 each. Group I received 3mg single IV dose of granisetron, group II received metoclopramide 10mg and group III received placebo in the form of normal saline immediately after the recovery from anaesthesia. The effects were assessed during the first 3 and the following 21 hours of postoperative period with the help of a scoring system. 0 – no emetic symptoms, 1- nausea and 2 – vomiting. The mean scores for the first3 hours were 0.8, 0.1, and 0.1 for placebo, metoclopramide and granisetron respectively and the corresponding scores in 3 – 24 hours duration were 0.6, 0.5 and 0.1.There was no difference in the scores during 0 – 3 hours but the scoring was significant during the 3 – 24 hours postoperative period and thus they concluded granisetron to be superior to metoclopramide in the prevention of PONV after anaesthesia.

Honkavaara[38] compared the efficacy of ondansetron 4mg and 8mg with placebo for controlling PONV in 75 patients undergoing middle ear surgery. The study was conducted in a double blinded randomized manner. They found that both the doses reduced PONV and also reduced the number of antiemetic needed per person.(droperidol : 0.72 in placebo group to 0.32 in both 4mg and 8mg groups). Ondansetron did not show any reduction of PONV in patients with history of motion sickness. It however reduced the patients suffering from PONV from 53% to 20% and

also reduced the requirement of rescue antiemetic from 53% to 17%. They concluded that ondansetron was an effective drug to be used in PONV and also concluded that 4mg ondansetron was the recommended dose as 8mg did not show any decrease of PONV or the need for rescue antiemetic.

Naguib et al [39] conducted a randomized double blinded study to compare the antiemetic efficacy of ondansetron 4mg, tropisetron 5mg and granisetron 3mg with that of metoclopramide 10mg and placebo .They considered 132 patients undergoing laparoscopic cholecystectomy. All the study drugs were given in IV route 10 minutes before the induction of anaesthesia. Direct questioning of patients was used to assess nausea and vomiting at 1, 4, 9, 12, 18 and 24 hours after the recovery from anaesthesia. The antiemetic used as rescue drug when required was metoclopramide. The percentages of emesis free patients were 65.5%, 52%, 48%, 29.2% and 27.6% in the ondansetron, granisetron, tropisetron, metoclopramide and placebo groups respectively. They concluded ondansetron to be a better antiemetic than metoclopramide or placebo. They had longer antiemetic activity too as the rescue antiemetics when required were considerably after longer duration of emesis free period. There was no significant statistical difference between ondansetron, tropisetron and granisetron groups.

Oksur et al [40] also studied the PONV control after laparoscopic cholecystectomy where they compared metoclopramide 10mg, granisetron 40mg; ondansetron 15mcg/kg given immediately before induction of anaesthesia. The nausea and vomiting scores of the first three hours

revealed that all the drugs had similar antiemetic effects. However in 4 – 24 hour period post-operatively metoclopramide group, has shown greater incidence of nausea and vomiting than the other groups.

Domino kb et al[41] conducted a meta-analysis for the efficacy of ondansetron, droperidol and metoclopramide in the prevention of post-operative nausea and vomiting. They performed a literature search for RCT using MEDLINE database and manual search. A total of 58 studies were considered. They found that ondansetron and droperidol was more effective than metoclopramide. Ondansetron was found a better antiemetic in children but both were found equally effective in adults.

Chen PP[42] compared the effectiveness of ondansetron and metoclopramide in preventing PONV in 50 patients undergoing major gynaecological procedures. The patients were randomized to receive either ondansetron 4mg or metoclopramide 10mg during closure of the pelvic peritoneum. The 24hour postoperative period was evaluated for PONV. In the first 24 hours 20% in ondansetron group and 33% in metoclopramide group vomited. However in the 4 – 12 hour period, 44 % of ondansetron and 37.5% in the metoclopramide group vomited respectively. Subsequently incidence was 52 and 37.5% respectively in the 12-24 hour period. The highest incidence of nausea was in the first 4 hour after surgery being 56% in ondansetron and 37.5% in the metoclopramide group. This decreased to 25% in both groups in the 12-24 hour period.

However Morris RW et al[43] did a multi-centre international placebo controlled study which evaluated the effect of ondansetron 4mg and metoclopramide 10mg in 1044 patients undergoing major gynaecological procedures under general anaesthesia and the results were different from the Chenn PP et al study. The patients were administered single I.V injection of the study drug prior to induction and the post-operative nausea and vomiting were assessed over the 24 hour post-operative period. Patients who received ondansetron experiencing no emetic episodes were (44%) while with metoclopramide it was 37% and only 23% of no emesis was experienced in placebo group. Similarly no nausea experienced in the ondansetron group was 32% and no nausea in the metoclopramide group was 24% and placebo was 16%. Thus they concluded ondansetron to be more effective antiemetic drug.

But again in a study by Monagle et al[44] the efficacy of ondansetron versus metoclopramide in preventing PONV in patients in undergoing gynaecological procedures was analyzed. They studied 90 patients, who were randomized to receive either ondansetron 4mg or metoclopramide 0.4mg /kg and the patients were assessed in the recovery room, the day ward and the following day after discharge. Both emetic and nausea scores were same in both the groups, with ondansetron group having a higher post-operative scores in the day ward ($p=0.001$). Thus they concluded metoclopramide was as effective as ondansetron to control PONV.

Watts SA[45] in a double blinded randomized study compared metoclopramide, ondansetron and cyclizine for its efficacy in controlling PONV in day case laparoscopic gynaecological procedures under general anaesthesia. 38 patients received no anti emetic. 166 patients were randomized equally to receive either metoclopramide 10mg or ondansetron 4mg or cyclizine 50mg immediately preinduction.50% of the patients in no antiemetic group had nausea and vomiting. While 24% in metoclopramide, 20% in ondansetron and 51% in cyclizine group had PONV, they concluded that there was no difference in the relative efficacy of ondansetron 4mg and metoclopramide 10mg.

In a study for prophylaxis for intraoperative nausea and vomiting during spinal anaesthesia for caesarean section ondansetron versus metoclopramide was studied by Garcia et al[46].They conducted a double blinded placebo controlled study of 150 ASA 1 and 2 women, divided into three groups of 50 each receiving placebo, metoclopramide and ondansetron. Nausea and vomiting occurred in 11.6% of the total case. They were absent in 91.8% of ondansetron and 91.6% of metoclopramide group. Only 60% of the placebo group was free from nausea and vomiting. They concluded that both drugs had an equal efficacy.

For the antiemetic efficacy in cardiac surgeries metoclopramide and ondansetron were compared by Wood Ward et al[47]. Ondansetron 16mg was administered to 115 patients and metoclopramide 15mg was given to 101 patients 1-2 hour before surgery. The evaluation for nausea and vomiting was done after extubation till discharge from intensive care or

for a period of 24 hours. Ondansetron had a higher incidence of nausea when compared to metoclopramide (49.6% vs 33.7% $p<0.05$) and vomiting (42.6% vs 24.8% $p<0.01$). There was no difference between groups in terms of number of patients who accepted post- operative antiemetics (ondansetron 43.4% and metoclopramide 32.6%). They concluded metoclopramide as a better agent in PONV.

In another study Pugh[48] compared prophylactic ondansetron and metoclopramide in preventing PONV in patients undergoing major neurosurgical procedures. 60 patients undergoing routine major neurosurgical procedures were considered in a prospective randomized double blind trial. The patients were randomly allocated into 2 groups and were given a standardized anaesthesia. Upon closing the dura mater the group A patients received an intravenous injection of metoclopramide 10mg and group B received ondansetron 8 mg intravenously. The patients were evaluated for 48 hours of postoperative period. The postoperative nausea and vomiting was less in metoclopramide group than in the ondansetron group. {9(30%) Vs. 17(56%) $p=0.038$}. They concluded with their study that ondansetron was not an appropriate drug for the prevention of postoperative nausea and vomiting when considering neurosurgical population.

Rose JB et al[49] studied the postoperative nausea and vomiting in post tonsillectomy pediatric patients in which they also compared the efficacy of ondansetron and metoclopramide in controlling PONV. They randomized 200 pre-adolescent children undergoing tonsillectomy and did

a double blinded placebo controlled prospective study and compared the antiemetic efficacy of one dose of metoclopramide 0.25mg/kg or ondansetron 0.15mg/kg given preoperatively intravenously with the two doses of the same drugs which was administered one hour postoperatively. There was significant reduction of PONV ($p < 0.005$) by two doses of either metoclopramide or ondansetron (18% and 8%) respectively when compared with placebo (50%), they concluded that two doses of metoclopramide 0.25mg/kg intravenously was as effective as two doses of ondansetron (0.15mg/kg) given intravenously.

A study by Tang et al[50] did an extensive research on ondansetron, for not just its effectiveness as an antiemetic but also the effect of timing of the drug . They also studied its cost effectiveness and cost benefit. For this they studied 164 women undergoing ambulatory laparoscopic gynaecological procedure in a placebo controlled double blinded study. The subjects were divided into 4 groups. Group A was given placebo, Group B was given 2mg ondansetron at the start and 2mg after the surgery, Group C was given 4mg I.V before induction and Group D was given 4mg after the surgery. The patients were monitored for 24 hours postoperatively. Compared to ondansetron 4mg given before the induction, ondansetron 4mg given after the surgery was more beneficial. This regime has highest patient satisfaction and lowest cost effectiveness ratio. Compared to placebo, ondansetron significantly reduced PONV and also facilitated recovery process by reducing the time of oral intake, ambulation and discharge readiness.

Launois et al[51] did a study comparing the cost effectiveness of ondansetron with that of metoclopramide when they are used in the treatment of PONV in patients undergoing elective surgery. They assessed intravenous ondansetron 4mg and intravenous metoclopramide 10 mg in the treatment of PONV in a prospective, randomized, double-blinded, parallel-group study in 60 hospital centres in France for its cost effectiveness. 746 adult patients with PONV within six hours of recovery from general anaesthesia were studied. The incidence of PONV and the medical resources used to treat it were collected. The incremental cost-effectiveness of ondansetron (additional cost of successful treatment) was the primary outcome measure. Mean cost effectiveness of efficient PONV management was calculated for both treatments. Costs were determined from the hospital perspective. The mean cost of PONV management per patient was 87.98 FF for ondansetron group and 70.86 FF for the group with metoclopramide. It was found that additional 17.12 FF will give each patient a 15.1% improved chance of successful control of nausea and vomiting. However this is less than the difference in the acquisition cost (52.11 FF) between the two groups. The mean cost effectiveness ratio was 190.43 FF for ondansetron and 227.85 FF for metoclopramide. In the ondansetron group the cost effectiveness ratio was lower because of the improved effectiveness. The lower cost of PONV management outweighed the increased drug acquisition cost.

In 2003, an international panel consisting of anaesthesiologists, surgeons and pharmacists had met to set guidelines in the management of

PONV. These guidelines were upgraded in 2006 and recently in 2014[52]. The salient guidelines were: To identify patients at risk for PONV in adult and pediatric population; approach for baseline reduction of risks for PONV; to identify the antiemetic with the most effective single therapy, to set combination therapy regimens for PONV prophylaxis, inclusion of nonpharmacologic approaches; recommend effective strategies in treatment of PONV when it occurs; to provide an algorithm for the management of individuals at higher risk for PONV and also to set up PONV prevention and treatment implementation in the clinical setting.

METHODLOGY

The present study was conducted in the department of anaesthesiology of Sree Mookambika Institute of Medical sciences, Kulasekharam, Kanyakumari. The study was conducted after getting clearance from the ethical committee of Sree Mookambika Institute of Medical Sciences. The data was collected from 84 ASA 1 and ASA 2 patients scheduled to undergo elective surgeries under general anaesthesia. The study was conducted over a period of 1 year, August 2013 to 2014.

Design of study:

Prospective, randomized, double blinded clinical trial with both the patient and the anaesthesia drug provider blinded to the study.

Sample Size:

The sample size of 84 was obtained by using the statistical program R using 93.1% as the benefitted incidence of using ondansetron and 66.7% as that for metoclopramide group .[15]

The study population (n=84) was divided into two groups consisting of equal number.

Group I: This group (n=42) consisted of patients receiving a combination of intravenous ranitidine 50 mg and intravenous metoclopramide 10 mg.

Group II: This group (n=42) consisted of patients receiving intravenous ondansetron 4 mg.

Inclusion criteria:

1. Consent of the patient
2. Patients undergoing surgery under general anaesthesia
3. Age group of above 18 years and below 60 years
4. Patients belonging to ASA 1- ASA 2

Exclusion criteria

1. Patients with hepatic, renal, neurological and endocrine abnormalities
2. Documented hypersensitivity to any of the study drugs
3. Previous history of postoperative nausea and vomiting
4. History of motion sickness
5. Patients with history of vomiting or Ryle's tube in situ in the last 24 hours
6. Emergency surgeries
7. Full stomach
8. Patients with history of acid peptic diseases, parkinsonism and vertigo
9. Patients with history of antiemetic drug intake in the last 24 hours
10. Patients belonging to ASA 3 and ASA 4

METHODS

The study conducted was a prospective, randomized, double blinded clinical trial.

All patients were visited preoperatively on the night before surgery and a detailed history and a detailed evaluation was done. All routine investigations under the hospital protocol were done. The inclusion criteria were met and a written informed consent was taken from the

patient. The patients were advised to remain nil per oral after midnight. On the morning of surgery, randomization of the patients into the respective groups was done by closed envelope technique. Both the patient and the principle investigator were blinded to the study. The patient's baseline pulse rate and BP were recorded. An IV access using 18 G cannula was acquired.

The help of the anaesthesia technician was sort in administering the drug half an hour prior to induction. The patients were randomly allocated into group I or group II

1. Group I : those who received a combination of ranitidine 50 mg IV and metoclopramide 10 mg IV
2. Group II : those who received ondansetron 4mg IV

Just before induction, 1mg midazolam and 0.2mg of glycopyrrolate was given intravenously. Patient was induced with Propofol 2mg /kg IV, fentanyl 1 mcg/kg IV and scoline 0.5mg/kg was given. Laryngoscopy was done and patient was intubated with the proper sized cuffed endotracheal tube. Atracurium 0.5mg/kg IV was used as the muscle relaxant. Anaesthesia was maintained with N20 66%, O2 33%, Isoflurane 1- 2 % and intermittent doses of atracurium and fentanyl were given. The intra operative NIBP, pulse rate, ETCO2 and continuous ECG were monitored. Duration of surgery and anaesthesia were noted. After the surgery, the patient was reversed with glycopyrrolate 0.01 mg/kg and neostigmine 0.05 mg/kg and was extubated after being fully awake.

Post operatively, analgesia was maintained with diclofenac 75 mg IM. Post operatively all episodes of nausea ,vomiting and retching were recorded by direct questioning and cross verified with the nursing care staff.

These were assessed by a scoring method.

NAME	SCORE	RETCHING	SCORE	EMESIS	SCORE
None	0	None	0	None	0
Mild	1	Mild	1	Mild	1
Moderate	2	Moderate	2	Moderate	2
Severe	3	Severe	3	Severe	3

Any side effects and the use of rescue anti emetics (ondansetron 4mg) were also recorded. The number of the events was recorded in the initial first hour and the 24 hours post operatively.

Statistical analysis

The sample size was obtained using the statistical programme R version 3.1. The demographic data was expressed in number, percentage, mean and standard deviation. Numerical data was analyzed by using R software. To find the statistically significant between the groups Chi-square, Fisher exact test, Student t was applied. Odds ratio was applied to find the correlation. P value less than 0.05 ($P<0.05$) was considered statistically significant at 95% confidence interval. The statistical analysis was done using statistical programme R version 3.1.Microsoft Excel spread sheet was used for data entry. Microsoft Word and Excel were used for generating the graphs and tables.

RESULTS

Table-1: Demographic data of study groups

Demographic data	Group-I		Group-II	
	Number	Percentage (%)	Number	Percentage (%)
Age (years)				
18-38	19	45.24	27	64.26
39-59	20	47.62	12	28.56
More than 59	3	7.14	3	7.14
Gender				
Male	18	42.86	20	47.62
Female	24	57.14	22	52.38
Weight (Kg)				
40-60	24	57.14	27	64.28
61-80	16	38.1	15	35.71
Above 80	2	4.76	0	0

The demographic data in terms of age, gender and weight is expressed in numbers and percentages.

Considering age: in both Group I and Group II, there were less number of patients under age group of above 59 years (7.14% in each group). Similar number of patients was included in the group-I and group-II. But in Group-II (64.26%) more number of patients were in the age group between 18-38 years than in Group I (45.24%).

Considering gender: 18 (42.86%) and 20 (47.62%) males were included in Group-I and Group II respectively. In Group-I, 24 (57.14%) and Group-II, 22 (52.38%) females were included in the study.

Considering weight: Most of the patients were having weight between 40-60kgs in both groups, with Group I having 24 (57.14%) and Group II having 27 (64.28%).

The same is graphically represented as follows:

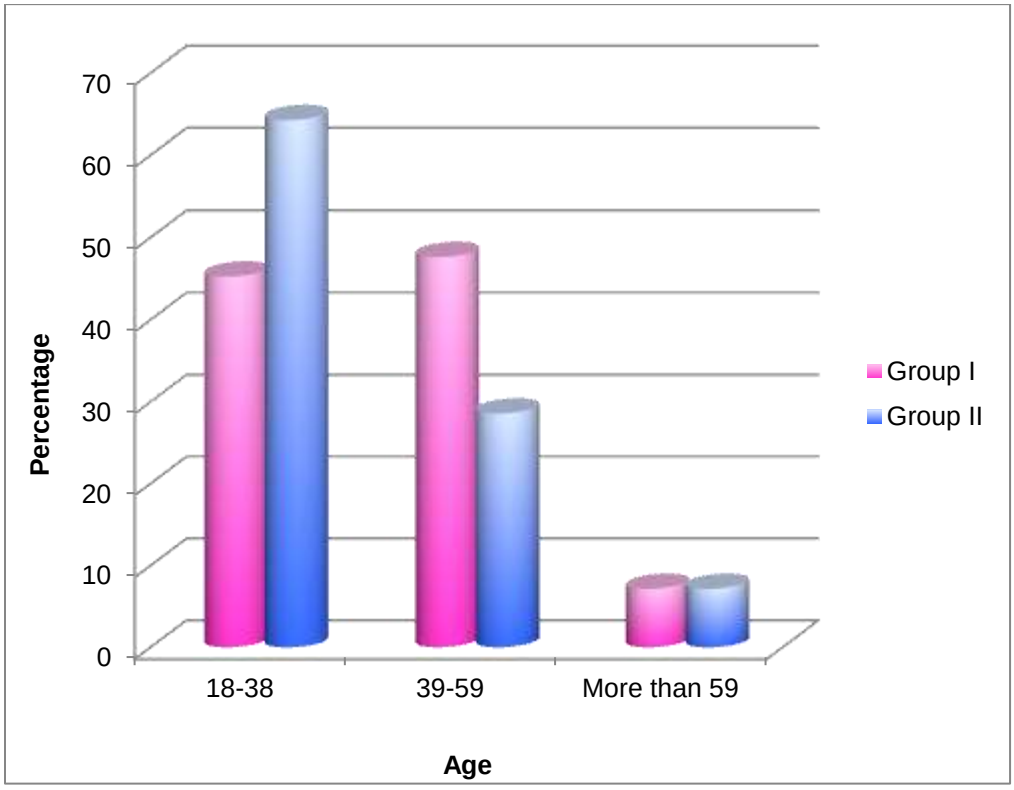

Figure-4: Distribution of Sample according to group and age

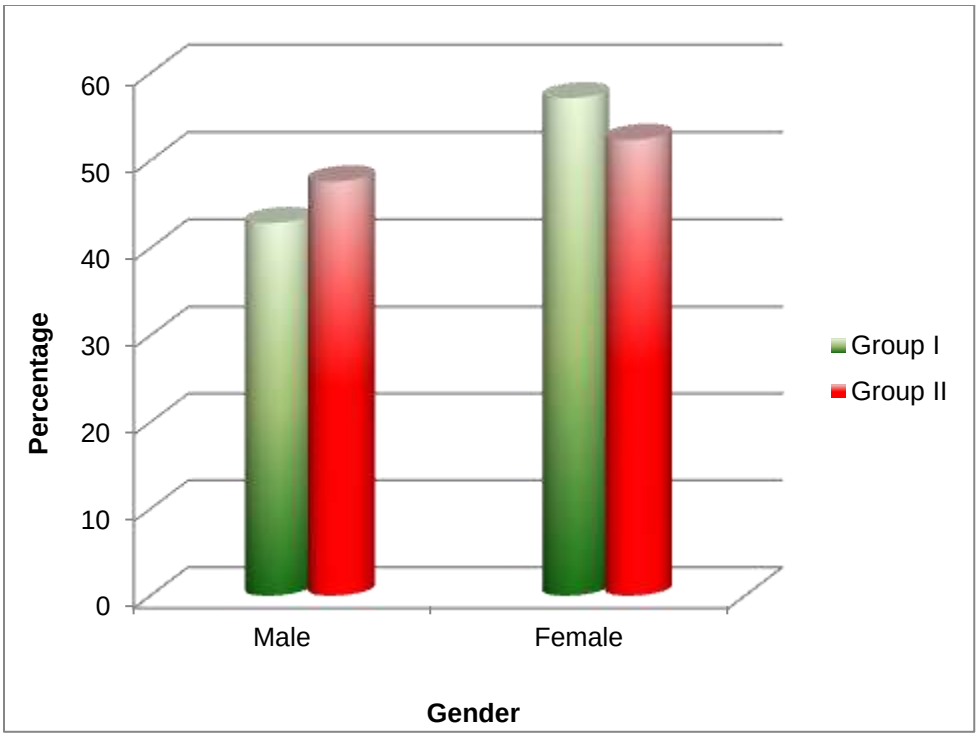

Figure 5: Distribution of sample according to group and gender

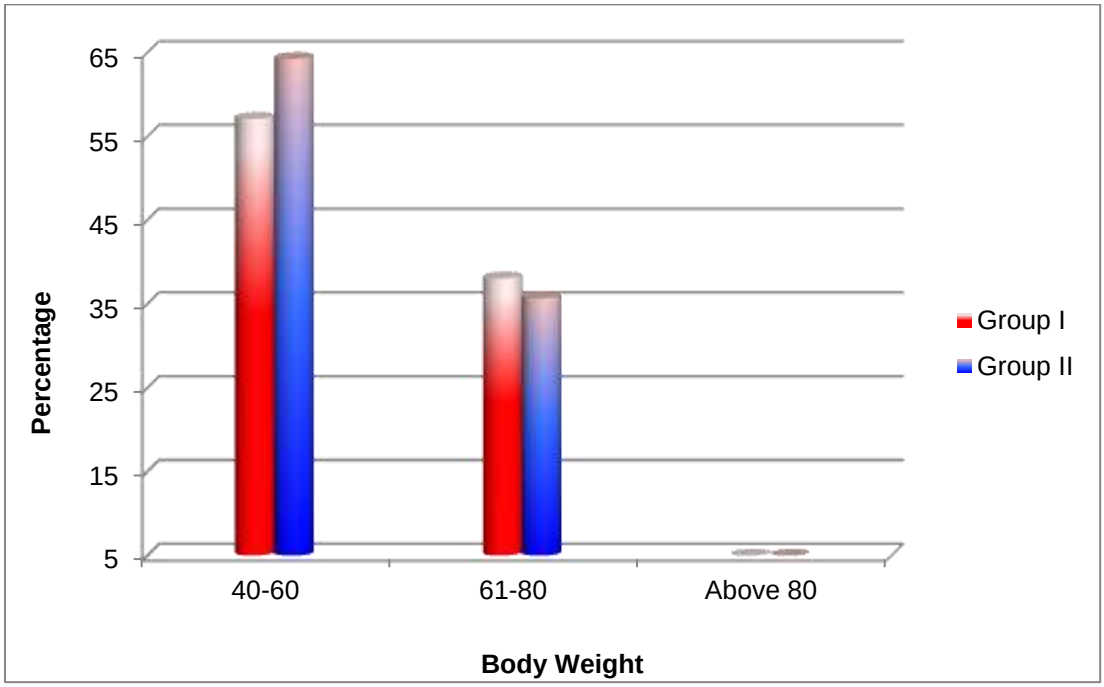

Figure 6: Distribution of sample according to group and weight

Table-2: Clinical data of study groups

S. No	Clinical observations	Group-I		Group-II	
		Number	Percentage (%)	Number	Percentage (%)
1.	**ASA Score**		*		*
	(1)	25	59.52	27	64.28
	(2)	17	40.48	15	35.71
2.	**Type of surgery**				
	Head and neck	15[#]	35.71	5	11.90
	Abdominal	7	16.67	4	9.52
	ENT	3	7.14	7	16.67
	OBG	2	4.76	5	11.90
	Breast	5	11.90	0	0
	Orthopedic	2	4.76	7	16.67
	Laparoscopic	4	9.52	12[$]	28.57
	Urology	4	9.52	2	4.76

(*P<0.05 significant, for ASA score with in the groups, but not between the groups, [#]P<0.05 significant, when comparing head and neck surgery with other surgeries within group-I, [$]P<0.05 significant, when comparing laparoscopic surgery with other surgeries within the group-II)

Table-2: Most of the patients were under ASA 1 in both the groups with Group I having 25 (59.52%) and Group II having 27 (64.28%) patients.

The same is represented graphically as follows:

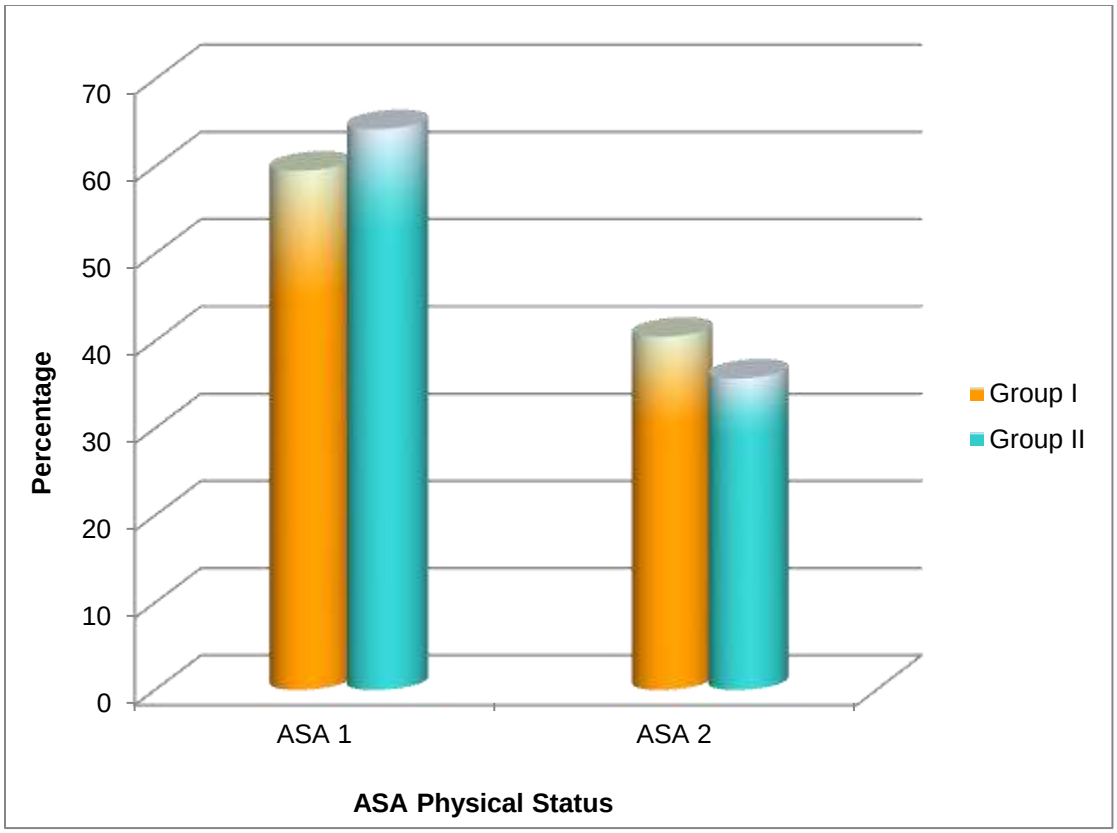

Figure 7: Distribution of sample according to group and ASA physical status

Considering the type of surgery in Group I, in comparison to other surgeries in the group most of the patients (35.71%) had undergone head and neck surgery, which was statistically significant. In group-II, in comparison to other surgeries most of the patients (28.57%) underwent laparoscopic surgery, which was statistically significant. In group-II there were no breast cancer patients.

The same is represented graphically as follows:

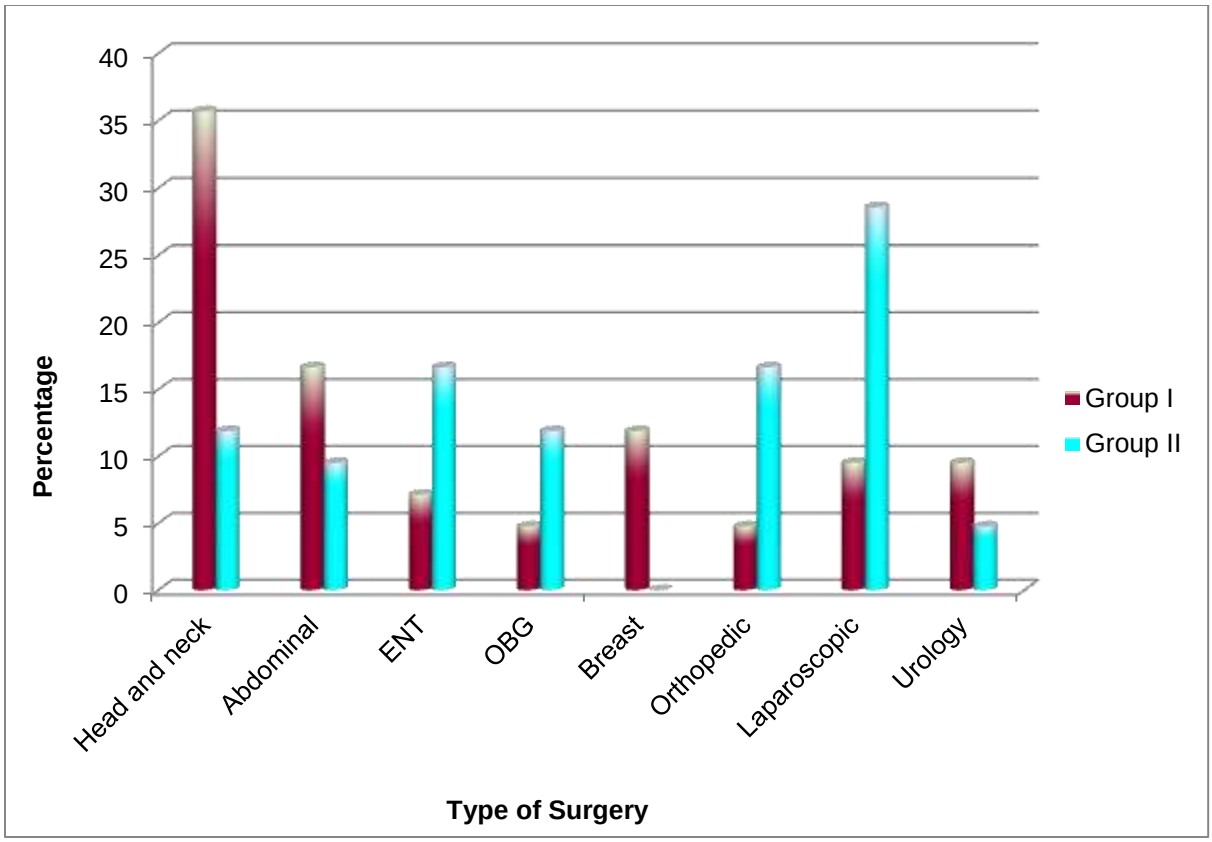

Figure 8 : Distribution of sample according to group and type of surgery

Table-3: Duration of surgery and anaesthesia of study groups

S. No	Clinical parameters	Group-I		Group-II	
		Number	Percentage (%)	Number	Percentage (%)
1.	**Duration of surgery**				
	1 hour	12	28.57	12	28.57
	2 hours	22	52.38	21	50
	3 hours	4	9.52	7	16.67
	4 hours	4	9.52	2	4.76
2.	**Duration of anaesthesia**				
	1 hour	2	4.76	2	4.76
	2 hours	21	50	21	50
	3 hours	14	33.33	12	28.57
	4 hours	4	9.52	6	14.28
	5 hours	1	2.38	1	2.38

Table-3: considering the duration of surgery in both groups equal number of patients underwent 1 hour surgery. Less number of patients underwent 3 hours surgery in Group I (9.52%) when compared to Group II (16.67%). Less number of patients underwent 2 and 4 hours surgery in Group II (50% and 4.76% respectively) when compared to Group I (52.38% and 9.52% respectively) which was significant when considering the 4 hours duration of surgery. The same is represented graphically as follows:

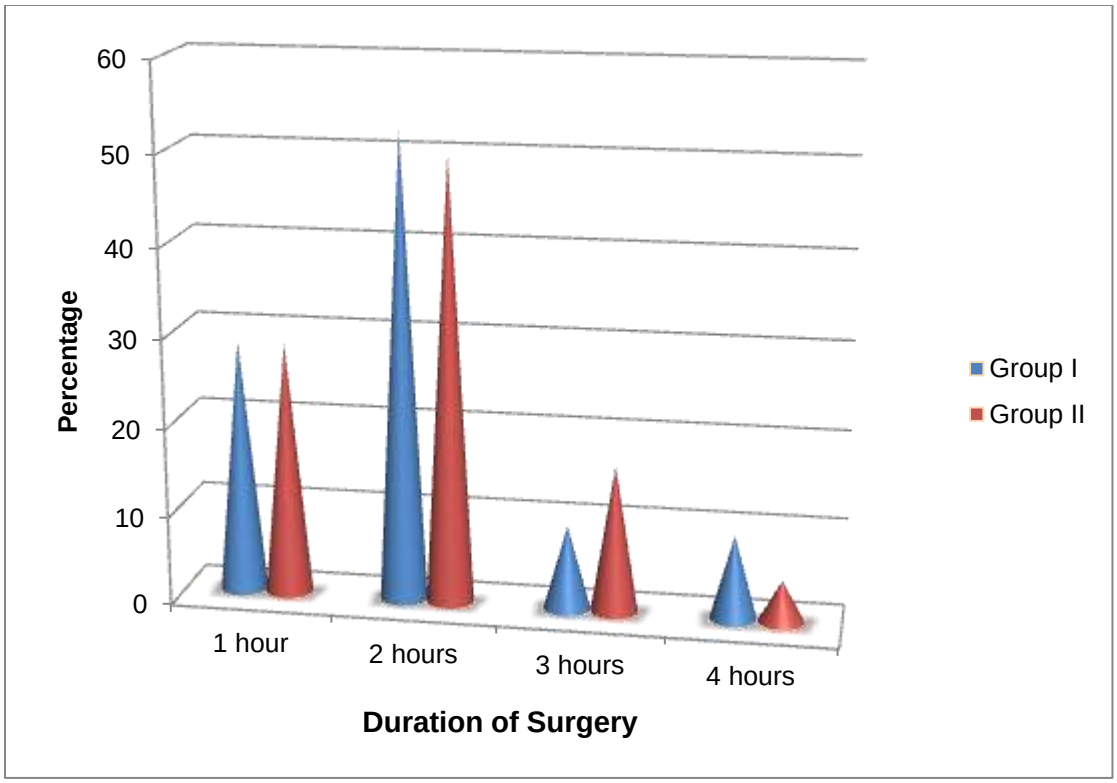

Figure 9: Distribution of sample according to group and duration of surgery

Considering the duration of anaesthesia similar number of patients underwent 1, 2 and 5 hour duration of anaesthesia in both the groups. In Group I, more number of patients (33.33%) underwent 3 hours duration of anaesthesia when compared to Group-II (28.57%). Group I less number of patients (9.52%) underwent 4 hours anaesthesia compared to Group-II (14.28%).

The same is represented graphically as follows:

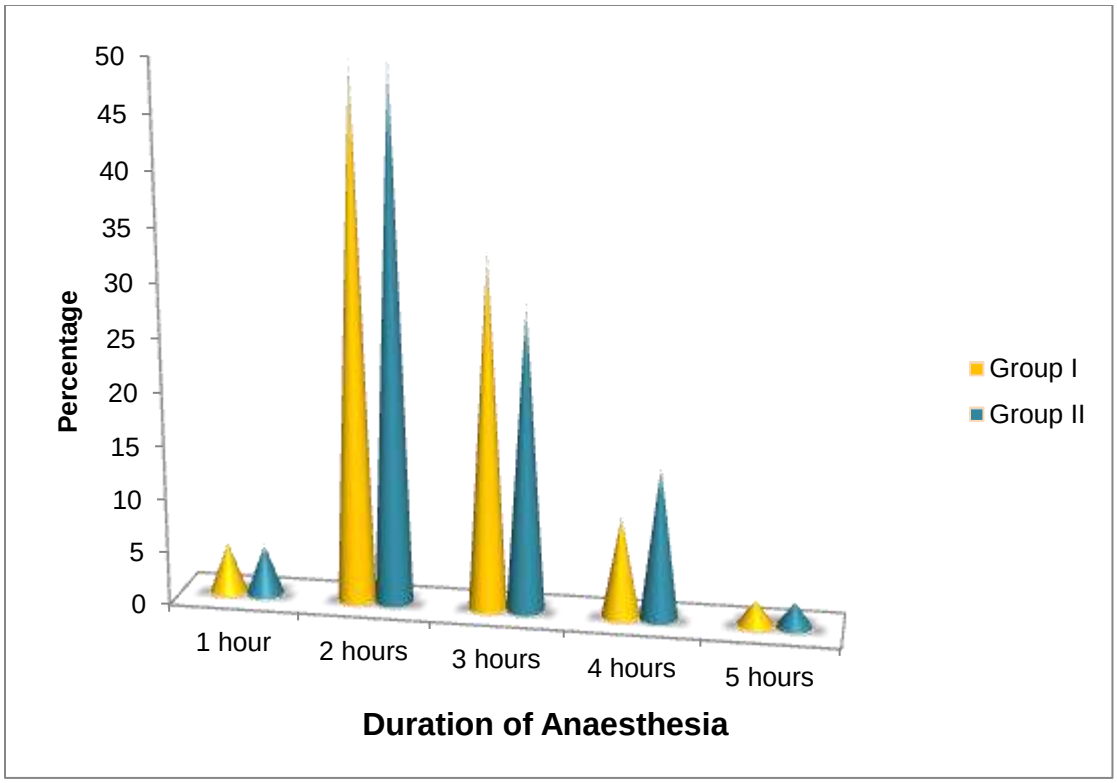

Figure 10: Distribution of sample according to group and duration of anaesthesia

Table 4: Mean and standard deviation for each factor in Group I and group II are given in the table below:

Observation	Age		Weight		Duration of Anaesthesia		Duration of Surgery	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Group I	39.23	12.56	61.76	10.82	130.11	51.15	105.83	49.66
Group II	35.76	13.36	58.76	8.70	131.07	46.18	107.98	44.79

Table 4:The mean age in the Group I was 39.23±12.56, in Group II it was 35.76±13.36.

The mean weight in Group I was 61.76±10.82, in Group II it was 58.76±8.70.

The mean duration of anaesthesia in Group I was 130.11±51.15, while in Group II it was 131.07±46.18

The mean duration of surgery in Group I was 105.83±49.66, while in Group II it was 107.98±44.79.

Table 5: Overall distribution of nausea and retching and vomiting

Observation	Nausea				Retching				Vomiting			
	Initial		After 24 hours		Initial		After 24 hours		Initial		After 24 hours	
	N	%	N	%	N	%	N	%	N	%	N	%
Present	24	28.57	9	10.71	11	13.1	3	3.57	16	19.05	5	5.95
Absent	60	71.43	75	89.29	73	86.9	81	96.43	68	80.95	79	94.05

Table 5: 28.57% patients presented with nausea in the initial hour which reduced to 10.71% after 24 hours. 13.1% patients presented with retching in the initial hour which reduced to 3.57% after 24 hours. 19.05% patients presented with vomiting in the initial hour which reduced to 5.95% after 24 hours.

Table 6: Correlation of various factors with frequency of vomiting, nausea and retching

Factor	Nausea initial	Nausea 24 hours	Vomiting initial	Vomiting 24 hours	Retching initial	Retching 24 hours
Age	0.8396	0.1558	0.6719	0.5858	1.2599	0.2708
Weight	0.7395	0.9617	0.1624	0.8059	0.311	0.5463
Gender*	0.0281	0.174	0.0248	0.372	0.0103	0.248
Duration of surgery	0.4313	0.9534	0.99	0.8877	0.7124	0.5292
Duration of anaesthesia	0.5019	0.9733	0.8653	0.9342	0.7737	0.4566

P<0.05 significant. Only gender showed to be a significant factor in enhancing nausea, vomiting and retching in the initial hour.

Table-7: Comparison of frequency of nausea and retching within the Group-I at initial and at 24 hours

Observation	Nausea		Retching	
	Initial	24 hours	Initial	24 hours
	Number	Number	Number	Number
Present	12 (28.57%)	4 (9.52%)	4 (9.52%)	2(4.76%)
Absent	30 (71.43%)	38 (90.48%)	38 (90.48%)	40(95.24%)
P value	0.02*	0.01*	0.01*	0.01*

(*P<0.05 significant, when comparing the frequency of presence and absence of nausea and retching at initial and at 24 hours within the group)

Table 7: Considering the initial hour: 12 patients (28.57%) had nausea while 30 (71.43%) people did not have nausea which was statistically significant. 4 (9.52%) people had retching while 38 (90.48%) people did not have retching which was statistically significant.

Considering the 24 hour period: even after 24 hours the same significant difference was observed.

Table-8: Comparison of frequency of nausea and retching within the Group-I at initial with 24 hours

Observation	Nausea		P value	Retching		P value
	Initial	24 hours		Initial	24 hours	
	Number	Number		Number	Number	
Present	12 (28.57%)	4 (9.52%)	0.01#	4 (9.52%)	2(4.76%)	0.856
Absent	30 (71.43%)	38 (90.48%)	0.01#	38 (90.48%)	40(95.24%)	0.567

(#P<0.05 significant when comparing the frequency of nausea and retching at initial with 24 hours within the group)

Table 8: considering nausea from initial to 24 hours, there was significant reduction of nausea frequency from the initial hour. Also the total number of people with absent nausea rose to 38 (90.48%) when compared to the initial 30(71.43%) which was significant.

Considering retching from initial to 24 hours, only 2(4.76%) had nausea while 40 (95.25%) did not have nausea.

Table-9: Comparison of frequency of nausea and retching within the Group-II at initial and at 24 hours.

Observation	Nausea		Retching	
	Initial	24 hours	Initial	24 hours
	Number	Number	Number	Number
Present	12 (28.57%)	5 (11.90%)	7 (16.67%)	1 (2.38%)
Absent	30 (71.43%)	37 (88.09%)	35 (83.33%)	41 (97.61%)
P value	0.01*	0.02*	0.01*	0.00*

(*P<0.05 significant when comparing frequency of nausea and retching at initial and at 24 hours within the Group II)

Table 9; considering the initial hour 12 (28.57%) patients were present with nausea and in 30 (71.43%) patients there was absence of nausea which was statistically significant.

Considering retching at initial hour, 7 (16.67%) patients had retching while 35 (83.33%) patients did not have retching which was statistically significant.

Considering the 24 hours : 37(88.09%) patients did not have nausea which was significant. 41 (97.61%) patients did not have retching which was significant.

Table-10: Comparison of frequency of nausea and retching within the Group-II at initial with 24 hours

Observation	Nausea		P value	Retching		P value
	Initial	24 hours		Initial	24 hours	
	Number	Number		Number	Number	
Present	12 (28.57%)	5 (11.90%)	0.02#	7 (16.67%)	1 (2.38%)	0.01#
Absent	30 (71.43%)	37 (88.09%)	0.678	35 (83.33%)	41 (97.61%)	0.467

(#P<0.05 significant when comparing frequency of nausea and retching at initial with 24 hours within the Group-II)

Table 10: considering the frequency of nausea from initial to 24 hours, the nausea frequency reduced from 12 (28.57%) in the initial to 5 (11.90%) in the 24 hour which was significant. The retching frequency also decreased to 1 (2.38%) after 24 hours when compared to the initial 7 (16.67%) which was significant.

Table-11: Comparison of frequency of nausea between the group-I and group-II at initial and during 24 hours

Groups	Nausea		
	Initial	24 hours	% of reduction
Group-I	12	4	66.66
Group-II	12	5	58.33
P value	0.956	0.845	0.476

p>0.5 not significant when comparing nausea in Group I with Group II

Figure-11: Comparison of frequency of nausea between the Group-I and Group-II at initial and 24 hours

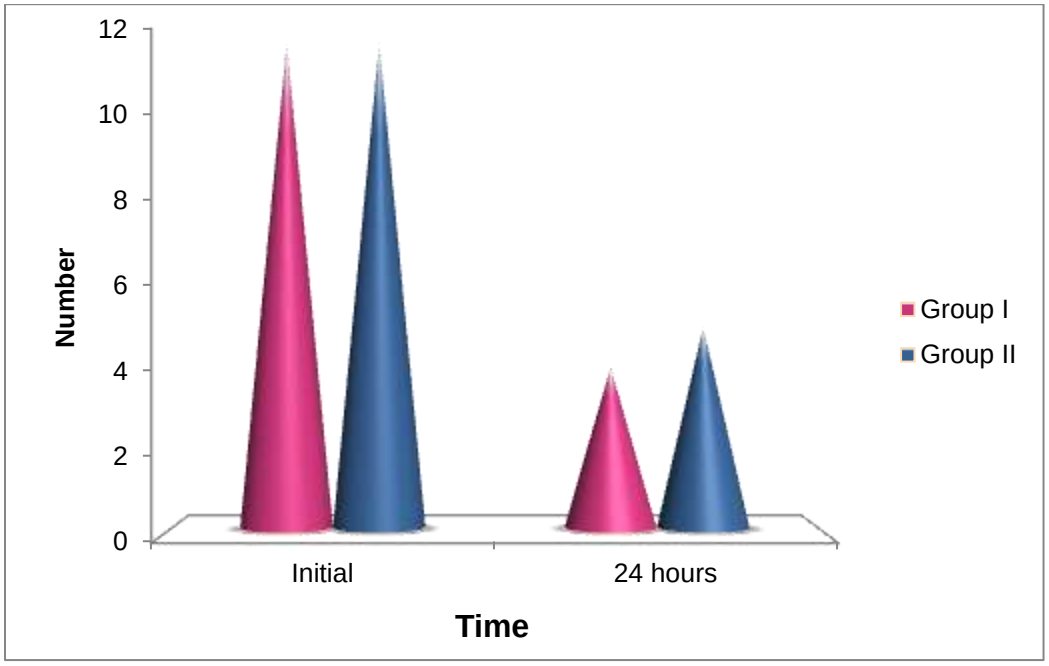

Table 11 and Figure 11: in the initial hour there were equal number 12 (28.57%) of patients with nausea in both the groups. But in 24 hours the nausea was present in 5 patients in Group II while in Group I nausea was present in only 4 patients. The reduction however was not statistically significant being 66.66% in Group I and 58.33% in Group II. Therefore neither of the group was superior to the other.

Table-12: Comparison of frequency of retching between the group-I and group-II at initial and during 24 hours

Groups	Retching		
	Initial	24 hours	% of reduction
Group-I	4*	2	50.00
Group-II	7	1	85.71*
P value	0.04	0.458	0.02

(*P<0.05 significant when comparing retching in Group-I with Group-II)

Figure-12: Comparison of frequency of retching between the Group-I and Group-II at initial and 24 hours

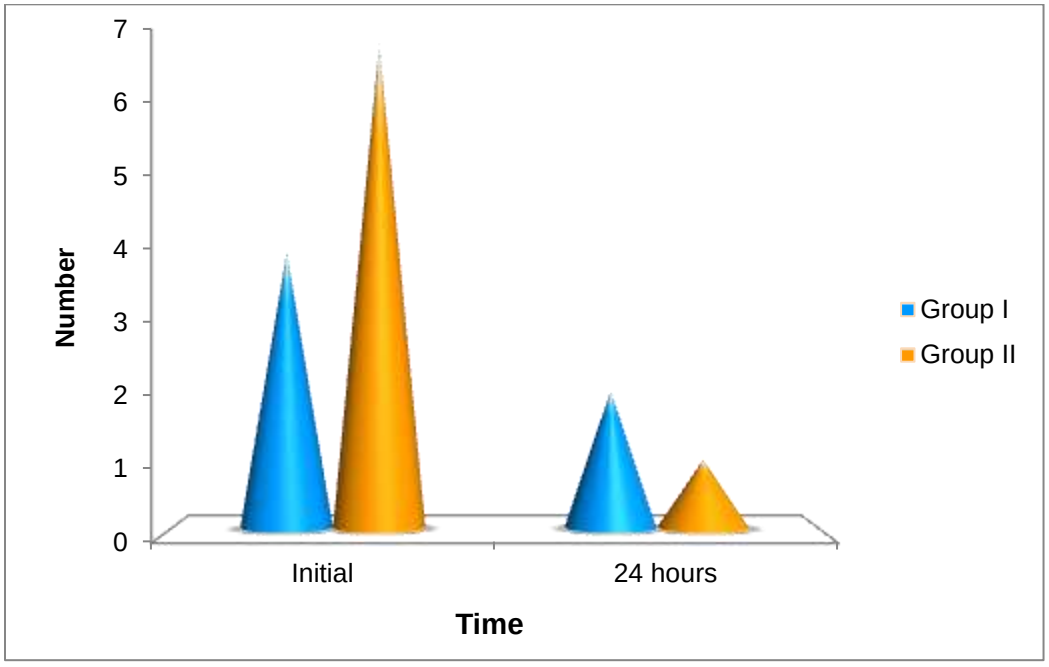

Table 12 and Figure 12 : Only 4 patients had retching in Group I(9.52%) when compared to 7 patients in Group II (16.67%)during the initial hour which was significant statistically(with p<0.05). After 24

hours 2(4.76%) patients in Group I and 1(2.38%) patient in Group II had retching which was not significant. After 24 hours 85.71% patients had reduction of retching in Group II compared to 50 % in Group I which was statistically significant. Therefore both groups had statistically significant effect in controlling retching but at different time intervals, with Group I having more number of retch free period in the initial hour and Group II having better retch reduction in 24 hours' time interval. Thus both are efficient in controlling the retch.

Table-13: Comparison of frequency of vomiting at the initial hour, at 24 hour within the Group-I

Observation	**Vomiting**	
	Initial	**24 hours**
	Number	**Number**
Present	10 (23.80%)	2(4.76%)
Absent	32 (76.19%)	40 (95.24%)
P value	0.02*	0.01*

(*P<0.05 significant when comparing frequency of vomiting at initial, at 24 hours in the Group-I)

Table 13:during the initial hour 32 (76.19%) patients had absence of vomiting which was statistically significant and after 24 hours 40 (95.24%) patients had absence of vomiting which was statistically significant.

Table-14: Comparison of frequency of vomiting from the initial hour to 24 hours within the Group-I patients

Observation	Vomiting		P value
	Initial	24 hours	
	Number	Number	
Present	10 (23.80%)	2 (4.76%)	0.01[#]
Absent	32 (76.19%)	40 (95.24%)	0.02[#]

([#]P<0.05 significant when comparing frequency of vomiting from initial to 24 hours in the Group-I)

Table 14: compared to the 10 (23.80%) patients with vomiting in the initial hour only 2 (4.76%) had vomiting in 24 hours which was statistically significant. Compared to 32 (76.19%) in the initial hour, 40 (95.24%) patients did not have vomiting in 24 hours which was significant statistically.

Table-15: Comparison of frequency of vomiting at initial, at 24 hours within the Group-II patients

Observation	Vomiting	
	Initial	24 hours
	Number	Number
Present	6 (14.28%)	3 (7.14%)
Absent	36 (85.71 %)	39 (92.85%)
P value	0.02*	0.02*

(*P<0.05 significant when comparing the frequency vomiting at initial, at 24 hours in the Group-II)

Table 15: considering the initial hour 36 (85.71 %) patients did not have vomiting and only 6 (14.28%) patients had vomiting which was significant. Considering the 24 hours, 39 (92.85%) patients did not have vomiting and only 3 (7.14%) patients had vomiting which was significant.

Table-16: Comparison of frequency of vomiting from the initial hour to 24 hour within the Group-II patients

Observation	Vomiting		P value
	Initial	After 24 hours	
	Number	Number	
Present	6 (14.28%)	3 (7.14%)	0.789
Absent	36 (85.71%)	39 (92.85%)	0.534

(P>0.05 no significance when comparing the frequency of vomiting from initial to 24 hours in the group-II)

Table 16: there was no statistically significant reduction in presence of vomiting after 24 hours when compared to the initial hour. There was also no statistically significant increase in the frequency of absent vomiting after 24 hours.

Table-17: Comparison of frequency of vomiting between the group-I and group-II at initial and 24 hours

Groups	Vomiting		
	Initial	24 hours	% of reduction
Group-I	10	2	80.00*
Group-II	6*	3	50.00
P value	0.05	0.73	0.04

(P>0.05 not significant when comparing frequency of vomiting in Group-I with Group-II at 24 hours and P<0.05 significant when comparing

frequency of vomiting in Group-I with Group-II in initial hour and when considering the reduction of vomiting)

Figure-13: Comparison of frequency of vomiting between the group-I and group-II at initial and during 24 hours

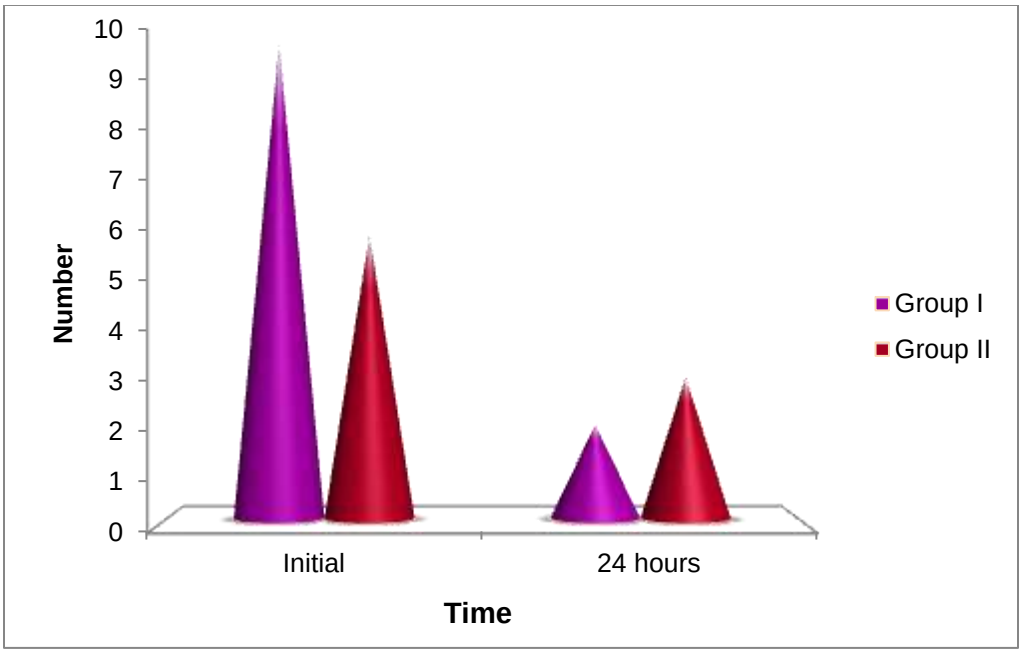

Table 17 and Figure 13: **In Group II only 6** (14.28%) patients had vomiting when compared to the 10 (23.80%) in Group I in the initial hour which was significant. But after 24 hours Group I had only 2(4.476%) patients with vomiting while in Group II 3(7.14%) patients had vomiting. While considering the reduction, Group I reduced vomiting in 80% and Group II reduced in 50% which was significant. Therefore though Group II significantly controlled vomiting in the initial hour, it was Group I that had a significant reduction in 24 hours.

Table-18: Comparison of addition of other rescue antiemetic and complications for the Group-I and Group-II

Other	Group-I		Group-II	
	Number	Percentage (%)	Number	Percentage (%)
Rescue antiemetic	1	2.38	2	4.76
Adverse effect	1	2.38	1	2.38

Table-18: In group-I only one patient had other rescue anti-emetic and side effect of abdominal discomfort. But in group-II, 2 patients had other rescue anti-emetic and 1 patient had side effect of headache but these were statistically insignificant values with P>0.

Table-19: Multiple comparison frequency of presence of nausea, vomiting and retching at different time intervals

Groups	Time period	NAUSEA	VOMITING	RETC
Group-I	**Initial**	12	10	4
Group-I	**24 hours**	4*	2*	2
Group-II	**Initial**	$12^{\#}$	$6^{\#}$	$7^{\#}$
Group-II	**24 hours**	$5^{*,\$}$	$3^{*,\$}$	$1^{\$}$

(*P<0.05 significant when comparing the frequency of number of patients with nausea, vomiting and retching in group-I initial with other time interval, $^{\#}$P<0.05 significant when comparing frequency of number of patients with nausea, vomiting and retching in group-I 24hours with other

time intervals, $P<0.05 significant when comparing frequency of number of patients with nausea, vomiting and retching in group-II initial with other time intervals)

Table 19: when considering Group I initial: there was significant reduction of nausea when compared with Group I after 24 hour and when compared to Group II after 24 hours. There was significant reduction of vomiting when compared to Group I after 24 hours and Group II after 24 hours. There was no significant reduction of retching.

When considering Group I after 24 hours: there was significant reduction of nausea when compared with Group II initial. There was significant reduction of vomiting when compared with Group II initial. There was significant reduction of retching when compared to Group II initial.

When considering Group II initial: it showed significant reduction of nausea, vomiting and retching when compared to Group II after 24 hours

DISCUSSION

PONV is one of the most dreaded complications of anaesthesia which is particularly high after general anaesthesia. It not only has a physical but also metabolic and psychological effects.[9] The incidence of PONV still remains high at about 20 -30 %[2,3]. In a study by Patel et al[15], which considered the pediatric age group, 33% of overnight admissions were due to PONV. In our study however the pediatric age group was excluded. The incidence of nausea ranging from the initial first hour up to 24 hours was about 28.57 to 10.71 %, that of retching was 13.1 to 3.51% and that of vomiting was 19.05 to 5.95%.

The presence of such a high incidence is not due to the absence of antiemetics but due to the multifactorial origin of PONV[2,3]. There are a wide range of antiemetics available for the treatment of PONV, but it is constantly needed to review these drugs not just to upgrade the effectiveness of the drug but also to contain the cost of PONV treatment. PONV leads to such a distressing scenario that patients are willing to pay up to $100 for the effective treatment [1]. But it is unethical to put such an additional economical and physical strain on the patients. Therefore it is required that cost and treatment effective drugs should be used.

In this study metoclopramide in combination with ranitidine was compared with ondansetron for its efficacy in PONV treatment occurring after general anaesthesia. The high incidence of PONV did not justify the usage of placebo in our study and was thus avoided. There are numerous

factors that can influence PONV, which can be patient related like age ,gender ,weight ,relevant previous history of nausea and vomiting or the factors could be surgery related [2,3,7,11]. In the present study many factors like age, weight, duration of surgery and duration of anaesthesia showed no influence on the PONV incidence. However gender was found to be a statistically significant factor in PONV. Female gender is considered as an independent risk factor for PONV as shown in the simplified risk factors of PONV by Apfel et al[12] .

The sample size of the present study was 84 which was similar to the sample size in the study by Leeser[25]. The dosage for the study drugs were obtained from the previous established dosages. The dose of metoclopramide was obtained with reference to the meta analysis by Henzi[18] in 1999, Mishriky[16] in 2012 and de Oliveira[17] in 2012. The dose of ranitidine was taken from the textbook information [13,14]. The dosage of ondansetron was taken from the study by Kaasa[31], Aboulwiah[26], Launois[51]. Metoclopramide is a prokinetic drug belonging to the benzamide group [2,3,13]. Ranitidine is a H2 receptor blocker[13,14]. Ondansetron is a highly selective $5HT_3$ receptor antagonist[13,14]. The drugs were given prior to the induction of anaesthesia which was similar to what was done by Oksuz[40], Morris[43], Watts[45], Garcia[46], Nozaki[23], de Oliveira[17]. The anaesthetic technique was standardized for all patients and controlled ventilation was provided. The data collected from the postoperative period was collected and then

statistically analyzed. A successful PONV treatment is considered by the complete control or absence of nausea, retching and vomiting.

These drugs were chosen for the study because for over 50 years metoclopramide had been used in the treatment of PONV. But of recent their effectiveness has been overshadowed by other drugs like 5HT3 blockers which claim to be superior in its efficacy in the treatment of PONV. But in the study by Mishriky[16] and Habib[18] in 2012, it was shown that 10 mg of metoclopramide when given did bring in a reduction of PONV . In this present study too it was shown that metoclopramide did significantly reduce the incidence of nausea, retching and vomiting. In our study too it was found that metoclopramide was effective in reducing the incidence of PONV. In this study, nausea was absent in 90.48%, retching was absent in 95.24% while vomiting was absent in 95.24% of patients when considering the 24 hour postoperative period. However this result differed from the studies by Fuji[37] where they claimed that metoclopramide was an ineffective antiemetic agent .Another author de Oliveira[17] in 2012 challenged the Fuji studies and had conducted a meta-analysis in which the antiemetic effect of metoclopramide was analyzed .The conclusion of the meta analysis was that metoclopramide was an effective antiemetic agent .Our study too had the same analysis.

But in our study it was not just metoclopramide that was used but instead a combination of metoclopramide with ranitidine was considered in the first group. The basis of combining another drug with metoclopramide was on the fact that combination of drugs have better

chances in reduction of PONV as outlined in the guidelines of PONV management[52]. Ranitidine an H2 blocker in combination with metoclopramide have been studied by William Pond [19] in 1987, however this study was conducted with the aim of analyzing the efficacy of this combination in preventing aspiration pneumonitis. However during their study, the efficacy of this combination in the prevention of postoperative nausea and vomiting was also observed. Our study took note of this useful finding and reached a similar conclusion. Moreover in a study by Cozanitis[21] also, it was shown that ranitidine reduced PONV when compared to placebo. Also in the study by Doenicke[22] where the effect of H1 and H2 blocker's benefit in PONV was compared to placebo it showed that H1 and H2 blockers reduced PONV with the incidence of PONV being only 8.5%, 6.8% and 5.4% with respect to the different combinations of H1 and H2 blockers that was used in the study. Even in our study in the group I which contained the H2 blocker, ranitidine the incidence of nausea was 9.52%, vomiting was 4.76%, and retching was 4.76 % when considering the PONV prevalence after 24 hours.

The second group in our study had ondansetron which is a 5HT3 blocker which is considered as a very efficient antiemetic agent. Leeser[25] did a study in 84 patients and divided them into two equal groups containing 42 patients each and studied ondansetron against placebo in controlling PONV. Leeser[25] found the incidence of nausea and vomiting was 17 and 12 % in the initial postoperative period and 29 and 26% in the 24 hour postoperative period. In our study too, 84 patients

were considered, out of which 42 fell in the ondansetron group. In our study the incidence of nausea was 28.57% in the initial hour and 11.90% after the 24 hour postoperative period and vomiting incidence was 23.80% in the initial hour and 4.76% after the 24 hour postoperative period. Both Leeser's and our study had the same conclusion that ondansetron was an effective agent in reducing PONV. Similarly the study by Honkavaara showed that ondansetron was effective in reducing PONV from 53 to 20%. In our study it was shown that ondansetron reduced nausea from the initial hour 28.57% to 11.90% in the 24 hour postoperative period while retching was reduced from 16.67% in the initial hour to 2.38% in 24 hour postoperative period and the incidence of vomiting was reduced from 14.28 % in the initial hour to 7.14% in 24 hour postoperative period.

Now coming to the comparison of the two study drug group , many studies such as that by Sarkar[27], Polati[28],Vishal Gupta[30], Kaasa[31] ,Sandhu[32], Sanjul[33] and Kulsoom[35] have concluded that ondansetron was a better antiemetic agent than metoclopramide.

However studies by Woodwand[47], Pugh[48] concluded metoclopramide to be a better agent. But the studies by Chen[42], Monagle[44], Watts[45], Gracia[46] and Rose[49] concluded both the drugs to be equally efficient.

In our study too the findings were towards both groups of drugs being equally efficient in controlling PONV. The salient findings in our study were:

1. In considering nausea in the metoclopramide group, in the initial postoperative period it was 28.57% which became 9.52% in the 24 hour postoperative period. In the ondansetron group too in the initial hour nausea was present in 28.57% which became 11.90% in the 24 hour postoperative period.

   When comparing the nausea reduction in both the groups, though metoclopramide ranitidine reduced nausea in 66.66% of patients and ondansetron reduced in only 58.33% this was not found statistically significant.

2. When considering retching, though in the initial hour metoclopramide ranitidine group had retching only in 9.52% of patients ondansetron had retching in 16.67% patients. This however became irrelevant after 24 hours where ondansetron reduced retching in 85.71% of the group while metoclopramide could reduce in only 50%.

3. When considering vomiting, in the initial hour ondansetron was found better with only 14.28 % patients having vomiting while metoclopramide ranitidine group had 23.80%. However after 24 hours significant reduction was seen in metoclopramide ranitidine group with a reduction of 80% when compared to ondansetron group which had only 50% reduction.

In the study by Chen [42] in the initial hour ondansetron was found as a better antiemetic with (20%) patients vomiting and in metoclopramide group 33% patients vomiting . However in the 24 hour postoperative

period metoclopramide group had only 37.5% patients vomiting while ondansetron had 44 %. Monagle [44] too had similar reports with both drugs being efficient but with ondansetron group having more emesis after 24 hours. In the study by Garcia [46] PONV was absent in 91.8% of ondansetron and 91.6% of metoclopramide group and they too concluded both drugs were equally efficient.

Not many studies have given enough reports on retching however in our study it was seen that only 9.52% had retching with metoclopramide ranitidine ,and 16.67% had retching with ondansetron when considering the initial hour but after 24 hours the reduction seen with ondansetron(85.71%) was greater than the reduction seen with metoclopramide ranitidine (50%). Only one patient (2.38%) had to be given rescue anti emetic in group I while two patients (4.76%) required antiemetics in group II which was similar to the study by Sanjul[33].

In both the groups both the drugs were well tolerated with only one patient complaining of abdominal discomfort in Group I and one patient complaining of headache in Group II. Thus there was no statistically significant difference in the efficacy of the two study group.

Adding a note on expense, Tang[50] in a study and Launois[51] in another study evaluated the cost effectiveness of ondansetron where they both concluded that ondansetron was more cost effective .In the study by Launois[51],which was conducted in France the mean cost of PONV treatment with ondansetron was 87.98 FF and that of metoclopramide 70.86 FF. But they evaluated that the higher cost of ondansetron treatment

could be overlooked because of the superiority of ondansetron in treatment of PONV .However with reference to our study both ondansetron and metoclopramide , ranitidine were found equally efficient in controlling PONV . So this study concludes that both metoclopramide-ranitidine combination and ondansetron can be used if cost effectiveness is to be considered along with effective management of PONV.

Limitations in the study were because of lack of adequate resources and time, issues such as economical impact of PONV as a whole and the expense imposed by the individual study drugs could not be evaluated. Also follow up of variables like delay of hospital discharge, sequelae of PONV were not studied which could be considered as the shortcomings of our study.

CONCLUSION

PONV is one of the most distressing consequences following general anaesthesia. Metoclopramide has been used previously for the treatment of PONV, but are now on a declining trend with the establishment of 5HT3 blockers .But metoclopramide was not only effective but also a cheap drug available for PONV treatment. Therefore in our study we studied a combination of metoclopramide 10 mg with ranitidine 50 mg for comparing its efficacy with 4 mg of ondansetron which is considered a better antiemetic drug. Both groups were given by the intravenous route prior to the induction in adult patients undergoing general anaesthesia. The patients were monitored postoperatively for the occurrence of nausea, retching and vomiting frequency which was recorded as that at initial first hour and that of 24 hours of postoperative period. It was statistically analyzed at the end of which we found and conclude that the combination of metoclopramide 10 mg and ranitidine 50 mg given intravenously was as efficient as ondansetron 4mg in their action to control PONV.

SUMMARY

PONV is multifactorial, hence requiring multifactorial treatment modalities especially in patients with high risks of developing PONV. After attaining the institutional ethics committee's approval 84 patients under ASA 1 and 2, in the age group of 18-60 years posted for elective surgeries under general anaesthesia were randomized into two equal groups of 42 each. Group I received a combination of metoclopramide 10 mg and ranitidine 50 mg I.V while Group II received ondansetron 4 mg I.V. Both drugs were given half an hour prior to induction. Standardization of anaesthetic technique was done and vitals were monitored. Postoperatively the episodes of nausea ,retching and vomiting were monitored for 24 hours and was recorded as reading at initial first hour and at the end of 24 hour postoperative period .Complete response to antiemetic prophylaxis defined by absence of nausea, retching and vomiting with no need of rescue antiemetic were noted .

The combination of metoclopramide 10 mg and ranitidine 50 mg was found to be as effective as 4mg ondansetron when given prior to induction. There was no significant adverse effect with either study group.

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APPENDIX I

INSTITUTIONAL HUMAN ETHICS COMMITTEE CLEARANCE

Sree Mookambika Institute of Medical Sciences
Kulasekharam (K.K District, TN) 629161
Phone No: 04651-280866. Fax No. 04651-280740

Institutional Human Ethics Committee

Ref. No. SMIMS/IHEC/2013/B/01 **Date: 2nd August 2013**

Certificate

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2013/B/01,** entitled "Comparison of Intravenous Ranitidine and Metoclopramide versus Intravenous Ondansetron in Preventing Post-operative Nausea and Vomiting Post General Anaesthesia" submitted by Dr. Mohsina Basheer, Postgraduate of Department of Anaesthesiology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 2nd of August 2013.

[This Institutional Human Ethics Committee is organized and operates according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

IHEC Date. 09/08/13

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor of Pharmacology and HOD
SMIMS, Kulasekharam (K.K District)
Tamil Nadu -629161

APPENDIX II

INFORMED WRITTEN CONSENT FORM

PART 1 OF 2

INFORMATION FOR PARTICIPANTS OF THE STUDY

Dear Volunteers,

We welcome you and thank you for your keen interest in participation in this research project. Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomforts, the precautions and the information about how this project will be carried out. It is important that you read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are free to ask the study personnel or the contact person mentioned below before you give consent and also at any time during the entire course of the project.

1. **Name of the Principal Investigator** :**Dr. Mohsina Basheer**
   Junior Resident,
   Department of Anaesthesiology,
   Sree Mookambika Institute of Medical Sciences, Kulasekharam.
2. **Name of the Guide** **:**Dr.G.Parvathy,
   Professor,
   Department of Anaesthesiology,
   Sree Mookambika Institute of Medical Sciences,
   Kulasekharam -629161.
3. **Name of Co- Guide** **:**Dr.V.G.Jayaprakash,
   Professor,
   Department of Anaesthesiology,
   Sree Mookambika Institute of Medical Sciences,
   Kulasekharam -629161.

4. **Institute** **:** Sree Mookambika Institute of Medical Sciences, Kulasekharam, Kanyakumari District – 629161 Tamil Nadu.

5. **Title of the study** **:**

Comparison of intravenous ranitidine and metoclopramide versus intravenous ondansetron in preventing post-operative nausea and vomiting post general anaesthesia.

6. **Background information** **:**

Postoperative nausea and vomiting (PONV) remain one of the most frequently encountered complications of after surgeries. And this may lead to increased hospital stay for patients. There are many drugs available to prevent this problem. This study is to find out the best available drug.

7. **Aims and Objectives** **:**

To compare the efficacy of ranitidine plus metaclopramide to that of ondansetron in controlling post-operative nausea vomiting in patients undergoing general anaesthesia.

8. **Scientific Justification of Study:**

There is a wide range of antiemetic drugs. The use of these drugs are however restricted by both cost and adverse effects and despite many studies, evidence base to support rational antiemetic treatment remains patchy. Therefore it becomes mandatory to frequently revive the studies to enroll the drugs with maximum efficacy.

9. **Procedure for the Study :**

The patients posted under general anaesthesia are reviewed overnight and kept under NPO since 12 midnight. On the morning of the surgery the patients after meeting the inclusion criteria can be randomly selected to fall into group I or group II. In each group we are required 42 patients. If the patient falls under group I, ranitidine 50mg and metoclopramide 10 mg is given half an hour before the surgery. If the patient is in group II, ondansetron 4mg will be given half an hour before the end of the surgery. Post operatively the patient will be monitored for 24 hours and the findings of which will be tabulated at 1hour and 24hour. The frequency of nausea, retching and vomiting will be scored as 0, 1, 2, 3 where:

0-none, 1- mild, 2-moderate,3-severe

10. **Expected risk for the participant:**

Few people may experience the following reactions;

a. Metoclopramide – fatigue, drowsiness, abdominal discomfort

b. Ranitidine - pain in muscles and joints, allergy

c. Ondansetron - Dizziness, headache, constipation

11. **Expected benefits of research for the participant:**

The participant will contribute to medical development and can also be benefitted in any future surgeries.

12. **Maintenance of Confidentiality :**

All data collected for the study will be kept confidentially and would reflect on general statistical evaluation only and would not reveal any personal details.

13. **Why have you been chosen to be in the study?**

- You are undergoing general anaesthesia and fulfill the criteria of selection.

14. **How many people will be in the study?** : 84

15. A**greement of compensation to the participant**: Yes.(by the investigator)

16. **Anticipated prorated payment, if any, to the participant(s) of the study:** Nil

17. **Can I withdraw from the study at any time during the study period?** : Yes

18. **If there is any new findings/information, would I be informed? :** Yes

19. **Expected duration of Participant's participation in the study:** 24 hours

20. **Whom do I contact for further information?: Dr. Mohsina Basheer**

For any study related queries, you are free to contact
Dr.Mohsina Basheer
Junior Resident
Department of Anaesthesiology
Sree Mookambika Institute of Medical Science, Kulasekharam
Mobile No: 9585782064
Email ID: mohsinabasheer23@gmail.com

Place: Kulasekharam

Date:

Signature of Principal Investigator

Signature of the Participant

CONSENT FORM

PART 2 OF 2

PARTICIPANTS CONSENT FORM

The details of the study have been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical science. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free in withdraw at any time, without giving any reason. Without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled "Comparison of intravenous ranitidine and metoclopramide versus intravenous ondansetron in preventing post-operative nausea and vomiting post general anaesthesia".

Serial No / Reference No:

Name of the Participant : Address of the Participant:

Contact Number of the Participant:

Signature/ Thumb impression of the participant/ Legal guardian

Witnesses:

1.

2.

Date:

Place:

APPENDIX III

PROFORMA FOR THE STUDY

Name of the patient:

Age:

Sex:

IP Number:

Surgical Diagnosis:

Proposed Surgery:

Relevant history:

History of drug allergy, drug reaction, previous surgeries:

GENERAL EXAMINATION

Height: Weight:

Pallor: Icterus: Cyanosis: Clubbing:

Lymphadenopathy:

Edema:

Any other relevant findings:

Pulse rate:

Blood pressure:

Temperature:

SYSTEMIC EXAMINATION

Examination of Cardiovascular system:

Examination of Respiratory system:

Examination of Gastrointestinal system:

Examination of Central Nervous system:

ASSESSMENT OF AIRWAY

Mallampati grade:

Thyro-mental distance:

Mouth opening distance:

Neck – range of motion:

Teeth:

Facial hair:

Morbid obesity:

Short muscular neck:

Micrognathia:

INVESTIGATIONS

Haematological:

Haemoglobin, total count, differential count, ESR

Bleeding time, clotting time

Blood sugar

Blood urea, Serum creatinine

HIV, HBsAg

Urine examination for sugar, albumin and microscopy

ECG

Chest X-ray- PA view if needed.

ASA physical status

Premedication:

Intra-operative monitoring: pulse rate, blood pressure, peripheral oxygen saturation, end tidal carbon dioxide.

APPENDIX IV

CASE RECORD FORM

STUDY GROUP:

Name of the patient: Age: Sex: Weight

IP Number: ASA: Type of Surgery:

Relevant history	Yes	No	Specify
• Previous History of nausea, vomiting and motion sickness. • Drug Intake • Drug allergy • Drug reaction • Previous surgeries • Co-morbidities • Others			

Duration of Anaesthesia :

Duration of Surgery :

	Drugs	Dose
Induction Agent		
Other drugs used		
Maintenance		

Intraoperative Monitoring

TIME	SPO_2	HR	BP	MAP	$ETCO_2$	TV

Post-Operative Monitoring: Initial Hour

OBSERVATION	NAUSEA	RETCHING	VOMITING
None			
Mild			
Moderate			
Severe			

Post-operative monitoring during 24 hours

OBSERVATION	NAUSEA	RETCHING	VOMITING
None			
Mild			
Moderate			
Severe			

Use of rescue antiemetic

Observation	Initial hour	During 24 Hours
Present		
Absent		

Adverse Effect

Absent:

Present:

Specify:

APPENDIX V

KEY TO THE MASTER CHART AND MASTER CHART

1. S. No		-	Serial number
2. IP no		-	In patient number
3. ARM		-	Group, where
			1=Group I
			2=Group II
4. NAME		-	Name of the patient
5. AGE		-	Age of the patient
6. SEX		-	Gender, where
			F= Female
			M=Male
7. Wt		-	Weight of the patient
8. ASA		-	American Society of Anaesthesiologists,
			where
			1= ASA 1
			2 = ASA 2
9. SURGERY		-	Type of surgery, where
	Head and neck	-	Surgeries involving the head and neck
	Abdominal	-	Abdominal surgeries
	ENT	-	Ear, nose and throat surgeries
	OBG	-	Obstetrics and gynaecological surgeries
	BREAST	-	Breast surgeries
	ORTHOPAEDIC	-	Orthopaedic surgeries

LAPAROSCOPIC - Laparoscopic surgeries

UROLOGY - Urological surgeries

10. DURS - Duration of surgery

11. DURA - Duration of anaesthesia

12. N1 - Nausea at initial hour, where

1. NO - absence of nausea

2. YES- presence of nausea

13. SN1 - Score of nausea at initial hour where

0= none

1=mild

2=moderate

3=severe

14. N24 - Nausea at 24 hours, where

1. NO = absence of nausea

2. YES = presence of nausea

15. SN24 - Score of nausea at initial hour where

0= none

1=mild

2=moderate

3=severe

16. NRESCUE - Use of rescue antiemetic for nausea

17. R1 - Retching at initial hour, where

1. NO = absence of retch

2. YES = presence of retch

18. SR1 - Score of retching at initial hour, where

0= none

1=mild

2=moderate

3=severe

19. R24 - Retching at 24 hours, where

1. NO = absence of retch

2. YES = presence of retch

20. SR24 - Score of retching at 24 hour, where

0= none

1=mild

2=moderate

3=severe

21. RRESCUE - Use of rescue antiemetic for retching

22. E1 - Emesis at initial hour, where

1. NO = absence of emesis

2. YES = presence of emesis

23. SE1 - Score of emesis at initial hour, where

0= none

1=mild

2=moderate

3=severe

24. E24 - Emesis at 24 hours, where

1. NO = absence of emesis

2. YES = presence of emesis

25. SE24 - Score of emesis at 24 hour, where

0= none

1=mild

2=moderate

3=severe

26. ERESCUE - Use of antiemetic for emesis

27. COMPLI - Complication

MASTER CHART

S.NO.	IP.No.	ARM	NAME	AGE	SEX	Wt	ASA	SURGERY	DurS	DurA	N1	SN1	N24	SN24	NRescue	R1	SR1	R24	SR24	R.Rescue	E1	SE1	E24	SE24	E.Rescue	COMPLI
1	173793	1	Mr. Unni	47	M	65	I	Head and neck	180	200	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
2	174202	1	Mrs. Mariya Azhagan	53	F	70	II	Head and neck	150	170	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
3	174724	1	Mr.Mani	50	M	75	II	Abdominal	90	115	2. Yes	2	1. No	0	1. No	1. No	0	1. No	0	1. No	2. Yes	2	1. No	0	1. No	0
4	176864	1	Mrs.Sinthiya	22	F	60	I	OBG	120	140	2. Yes	1	2. Yes	1	1. No	1. No	0	2. Yes	1	1. No	2. Yes	1	1. No	0	1. No	0
5	177161	1	Mrs.Jessy	42	F	60	I	Breast	30	50	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
6	178408	1	Mr.Teddy	42	M	70	I	Abdominal	60	80	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
7	178243	1	Mr.Vishnu	25	M	62	I	Abdominal	180	200	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
8	181997	1	Mrs.Vimala Devi	45	F	80	I	Head and neck	150	190	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
9	178888	1	Mrs.Shanthi	48	F	89	I	Abdominal	200	220	2. Yes	3	1. No	0	1. No	2. Yes	2	1. No	0	1. No	2. Yes	1	1. No	0	1. No	0
10	181422	1	Mr.Paul Raj	52	M	48	II	Urological	40	60	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
11	182921	1	Mr.Yesuratham	53	M	60	II	Head and neck	240	270	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
12	182931	1	Ms.Arebana	22	F	70	I	Head and neck	220	250	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
13	182925	1	Mrs.Thajeetha Beevi	40	F	70	I	Laproscopic	60	80	2. Yes	1	2. Yes	2	1. No	1. No	0	2. Yes	1	1. No	2. Yes	1	2. Yes	1	1. No	0
14	183136	1	Mrs.Lalithambika	34	F	54	II	Laproscopic	60	85	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
15	183164	1	Mrs.Sasikala	32	F	52	II	Laproscopic	60	80	2. Yes	2	1. No	0	1. No	1. No	0	1. No	0	1. No	2. Yes	1	1. No	0	1. No	0
16	185349	1	Mrs.Gomathy	39	F	52	II	Laproscopic	60	85	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
17	178597	1	Mr.Mariya Pocoliyan	46	M	75	II	Head and neck	95	115	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
18	181888	1	Mr.Albert	35	M	89	I	Urological	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
19	185796	1	Mrs.Majeeba	34	F	50	I	Head and neck	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
20	185507	1	Mrs.Shengabavati	38	F	70	I	Breast	90	110	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
21	186398	1	Mrs.Santhya	23	F	52	I	Abdominal	200	220	2. Yes	2	2. Yes	2	1. No	2. Yes	1	1. No	0	1. No	2. Yes	1	2. Yes	2	2. Yes	0
22	188225	1	Mr.Ajikumar	27	M	52	I	Head and neck	90	110	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
23	187831	1	Mr.Arul Pomani	32	M	65	I	ENT	110	135	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
24	189134	1	Mr.Abilash	22	M	60	I	Head and neck	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	discomfort
25	189352	1	Ms.Asha	21	F	50	I	Breast	50	75	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
26	189720	1	Mrs.Mahalekshmi	52	F	50	II	Head and neck	120	140	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	2. Yes	1	1. No	0	1. No	0
27	190301	1	Mrs.Nabeesha	40	F	56	II	Breast	100	120	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	2. Yes	1	1. No	0	1. No	0
28	191061	1	Mr.Ayyanswami	55	M	52	II	Urological	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
29	191604	1	Mr.Mathew	60	M	76	II	Ent	90	115	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
30	191159	1	Mrs.Saraswathy	49	F	53	I	OBG	90	115	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
31	193192	1	Ms.Rajayya	50	F	43	I	Ent	60	85	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
32	193007	1	Mrs. Mincy	24	F	70	I	Orthopaedic	90	130	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
33	195273	1	Mr. Mohandas	39	M	60	I	Head and neck	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
34	194805	1	Mrs.Kilbeth Beevi	53	F	70	II	Head and neck	110	130	2. Yes	2	1. No	0	1. No	2. Yes	1	1. No	0	1. No	2. Yes	2	1. No	0	1. No	0
35	196217	1	Ms.Prabha	26	F	60	I	Breast	50	65	N0	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
36	193820	1	Mr.Vijayakumar	64	M	57	II	Urological	60	85	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
37	197118	1	Mrs.Saroja	38	F	50	I	Head and neck	90	120	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
38	197120	1	Mr.Rajesh	20	M	60	I	Abdominal	60	80	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
39	197488	1	Mr.Jayapaul	59	M	65	II	Orthopaedic	90	110	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
40	200120	1	Ms.Kalpana	18	F	50	II	Head and neck	90	120	2. Yes	2	2. Yes	2	1. No	2. Yes	1	1. No	0	1. No	2. Yes	2	1. No	0	1. No	0
41	199542	1	Mrs.Kumari Thaagam	45	F	62	I	Head and neck	90	110	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
42	202756	1	Mr.Siddiq	32	M	60	II	Abdominal	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0

S.NO.	IP.No.	ARM	NAME	AGE	SEX	Wt	ASA	SURGERY	DurS	DurA	N1	SN1	N24	SN24	NRescue	R1	SR1	R24	SR24	R.Rescue	E1	SE1	E24	SE24	E.Rescue	COMPLI
43	166322	2	Vasudevan	65	M	60	II	Urology	150	170	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
44	174114	2	Archana	22	F	59	I	Laproscopic	90	120	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
45	174115	2	Beena Mol	26	F	61	I	Laproscopic	90	110	2. Yes	2	2. Yes	2	1. No	2. Yes	1	2. Yes	1	1. No	2. Yes	1	2. Yes	2	2. Yes	0
46	174118	2	Shobha	33	F	60	II	Ent	90	120	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
47	176715	2	Abser Khan	33	M	60	II	Ent	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
48	176527	2	Ponnupillai	65	M	58	II	Ent	120	140	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
49	185095	2	Deepa	31	F	58	I	OBG	90	110	2. Yes	1	1. No	0	1. No	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	0
50	182280	2	Shaiba	29	F	70	I	Laproscopic	60	80	2. Yes	1	1. No	0	1. No	2. Yes	1	1. No	0	1. No	2. Yes	1	1. No	0	1. No	0
51	182283	2	Sanjeetha	35	F	59	I	Laproscopic	45	60	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
52	176676	2	Raguvan	26	M	60	I	Abdominal	150	170	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
53	176272	2	Raveendran	30	M	50	I	Head and neck	140	165	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
54	185452	2	Sasikala	31	F	45	I	OBG	100	120	2. Yes	2	1. No	0	1. No	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	0
55	185463	2	Sajeela	32	F	65	II	Ent	120	140	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	Headache
56	185578	2	Jerina Banu	25	F	75	I	Laproscopic	90	110	2. Yes	1	2. Yes	1	1. No	2. Yes	1	1. No	0	1. No	2. Yes	1	1. No	0	1. No	0
57	177084	2	Sreekumar	48	M	60	I	Urology	150	175	2. Yes	1	2. Yes	1	1. No	2. Yes	1	1. No	0	1. No	2. Yes	1	1. No	0	1. No	0
58	186940	2	Rekha	24	F	54	I	Laproscopic	60	85	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
59	187548	2	Arumugam	43	M	54	II	Ent	200	220	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
60	186693	2	Latha	30	F	41	I	OBG	90	110	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
61	187800	2	Naveena	21	F	70	II	Laproscopic	60	85	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
62	178430	2	Pallammal	58	M	70	II	Orthopedic	120	145	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
63	180557	2	Ratheesh	27	M	65	II	Orthopedic	180	200	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
64	180559	2	Murukesan	59	M	70	I	Orthopedic	120	135	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
65	188684	2	Gayathridevi	29	F	61	I	OBG	60	80	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
66	190198	2	Mini	25	F	50	I	OBG	60	75	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
67	194858	2	Priya	32	F	61	I	Laproscopic	60	80	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
68	199153	2	Saranya	24	F	52	I	Abdominal	60	85	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
69	198625	2	Ponnamal	52	M	75	II	Abdominal	90	110	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
70	198732	2	Jini	30	F	64	I	Laproscopic	50	85	2. Yes	3	2. Yes	1	1. No	2. Yes	1	1. No	0	1. No	2. Yes	2	2. Yes	1	2. Yes	0
71	197661	2	Shincy	24	F	46	I	Laproscopic	60	80	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
72	197582	2	Pradeep	19	M	45	I	Ent	120	145	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
73	197012	2	Subith	18	M	66	I	Ent	180	200	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
74	181159	2	Christhu Rajan	45	M	60	II	Orthopedic	180	210	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
75	194828	2	Lekshmi	40	F	51	II	Laproscopic	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
76	194975	2	Jenifa	25	F	44	I	Laproscopic	60	75	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
77	201787	2	Usha	47	F	60	II	Head and neck	100	120	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
78	202442	2	Mani	53	M	49	II	Abdominal	120	140	2. Yes	2	2. Yes	1	1. No	1. No	0	1. No	0	1. No	1. No	0	2. Yes	1	1. No	0
79	202507	2	Krishnan	48	M	55	I	Head and neck	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
80	202568	2	Sanal	19	F	50	I	Head and neck	240	270	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
81	193008	2	Prasad	28	M	75	I	Orthopedic	120	150	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
82	188222	2	Murugayan	60	M	55	II	Orthopedic	60	80	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0
83	189335	2	Sukumaran	44	M	60	I	Head and neck	120	150	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	2. Yes	1	1. No	0	1. No	0
84	187739	2	Rajayyan	47	M	65	I	Orthopedic	120	150	2. Yes	1	1. No	0	1. No	1. No	0	1. No	0	1. No	1. No	0	1. No	0	1. No	0